REVIEW ARTICLE

Sleep disordered breathing in children

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Abstract

Sleep disordered breathing (SDB) in children has been recognized over the past two decades due to research and clinical advances in pediatric sleep medicine. Pediatric SDB comprises of central apnoea/hypoventilation, apnoea of prematuriry, the spectrum of obstructive sleep hypoventilation disorders and hypoventilation during sleep due to chronic pulmonary disease. Obstructive sleep hypoventilation syndromes have a clinical range from primary snoring, through upper airway resistance syndrome to obstructive sleep apnoea syndrome (OSAS). Though, the exact prevalence of SDB and obstructive sleep hypoventilation syndrome is not known, the prevalence of OSAS in children varies between 1-4%. Pathophysiology, clinical manifestation, diagnosis and treatment of pediatric SDB which differs from adult SDB is reviewed along with its recent advances.

Introduction

Sleep is a major physiological drive. An average child spends almost one half of his or her life asleep.[1] Sleep impacts almost all aspects of a child's functioning, thus the increased recognition and treatment of sleep disorders will positively affect a child's well-being. Although the association of obesity and sleep disordered breathing (SDB) was first noted by Charles Dickens in his description of Joe, an obese, hypersomnolent boy in the posthumous papers of the Pickwick Club more than 100 years ago, it is only in recent times that the extent of SDB in the paediatric population has been realised. [2] The term SDB in children refers to a group of respiratory disorders that occur or are exacerbated during sleep (box 1). These include the following: the spectrum of obstructive sleep hypoventilation disorders, central apnoea/hypoventilation, apnoea of prematuriry, and worsening of hypoventilation due to respiratory disease during sleep.

Box 1: Classification of pediatric Sleep Disordered Breathing

- Spectrum of obstructive sleep hypoventilation disorders
- Central apnoea/hypoventilation
- Apnoea of prematuriry
- Hypoventilation during sleep due to chronic pulmonary disease

Obsructive sleep hypoventilation syndrome (OSHS)

Obstructive sleep hypoventilation syndrome is a spectrum of disease which includes snoring, upper airway resistance syndrome (UARS), and obstructive sleep apnoea syndrome (box 2). Though, the pathophysiology of upper airway obstruction due to all the types of OSHS is similar; the clinical manifestation, diagnosis and management differ.

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Box 2: Classification of obstructive sleep hypoventilation disorders in children

- Snoring
- Upper airway resistance syndrome (UARS)
- Obstructive sleep apnoea syndrome

Snoring

There is no universal accepted, clear definition of snoring. The prevalence of habitual snoring as described by parents as "always snoring" ranges from 1.5 to 6 %. Parents reported "habitual snoring" range from 5-12 %.[3] Snoring in children does not require specific treatment unless it is associated with obstructive sleep apnoea.

Obstructive sleep apnoea syndrome

Definition

Obstructive sleep apnoea syndrome (OSAS) in children is a "disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns." [4, 5, 6]

Prevalence

Pediatric obstructive sleep apnoea has become widely recognized only in the last few decades as a likely cause of significant morbidity among children. There are numerous challenges including widely variable methodologies for collection of questionnaire data about symptomatology, definitions of habitual snoring, criteria for advancing to further diagnostic testing, and objective diagnostic criteria for SDB and OSAS. Hence, there is wide variation in prevalence in various studies. The prevalence of OSAS diagnosed by varying criteria on diagnostic studies ranges from 0.1 to 13%, [7, 8, 9] but most studies report a figure between 1-4%.[3] Relatively persuasive if not uniform evidence suggests that snoring and OSAS are more common among boys and among children who are heavier [10, 11] Severity of OSAS in obese children is proportional to the degree of obesity. [12, 13] The peak incidence of OSAS occurs between 2 to 8 years of age and parallels the prominent growth of lymphoid tissue around the airways during these years. Later onset of symptoms particularly when associated with obesity is common between school age and adolescent years. [4]

Pathophysiology

On the basis of relative contribution to the pathophysiology of OSAS by adenotonsillar hypertrophy and increased fat deposits in the upper airway structures, two distinct types of OSAS have been proposed by Capdevilla OS et al; one associated with marked lymphadenoid hypertrophy in the absence of obesity (type I), and the other associated primarily with obesity and with milder upper airway lymphadenoid hyperplasia (type II).[14] Another type though not as well developed includes variety of craniofacial and neuromuscular disorder (e.g. Crouzon and Alport syndromes, Pierre Robin syndrome, Goldenhar syndrome, achondroplasia, myelomeningocele and cerebral palsy) could be labeled as type III (Box 3).[15] OSAS in children with neuromuscular disorder is due to defect in pharyngeal dilator muscle action leading to increased collapsibility of the upper airway.

Box 3: Types of obstructive sleep apnoea syndrome in children based on pathophysiology

Type 1:	Associated with Lymphadenoid hypertrophy in the absence of obesity
Type 2:	Associated with Obesity with milder upper airway lymphadenoid hyperplasia
Type 3:	Associated with Craniofacial & neuromuscular disorder

Although childhood OSAS is associated with adenotonsillar hypertrophy, large tonsils and adenoid alone do not cause it. Patients with adenotonsillar hypertrophy and OSAS do not obstruct during wakefulness, studies have failed to show a correlation between upper airway/adenotonsillar size and OSAS and a small percentage of children with adenotonsillar hypertrophy with OSAS are not cured by adinotonsillar resection. Guilleminault[16] and colleagues reported a cohort of children who were cured of their OSAS by adenotonsillectomy, but developed a recurrence during adolescence. Thus, it appears that childhood OSAS is a dynamic process resulting from a combination of structural and neuromotor abnormalities, rather than from structural abnormalities alone.[17]

Clinical manifestation

Many of the clinical characteristics of pediatric OSAS differ from those of adult OSAS (Table1). Though, loud snoring and difficulty during breathing are common to both adult and children except for young infants,[4]

excessive daytime sleepiness is uncommon in children owing to difference in threshold for sleepiness between the two.[17, 18] OSAS children are mouth breathers and frequently have upper respiratory tract and ear infection. Neurocognitive deficits such as poor learning and behavioral manifestations are common in children being attributed to intermittent hypoxemia. Behavioral manifestations observed in children with OSAS are similar to attention deficit hyperreactive disorder which leads to poor academic performance. [19, 20, 21]

Physical examination

Children with OSAS are often reported to have delayed growth and impaired weight gain due to decreased levels of insulin-like growth factor-I. [22, 23] On the other hand, obesity in children increases the risk for OSAS by 4.5 fold.[11] Mouth breathing and adenoid facies may be seen. The Mallampatti classification is useful for assessment of older obese children. [24]

Consequences of pediatric OSAS

About three times increase in neurocognitive deficits such as poor learning and behavioral disturbances including restlessness, hyperactivity and aggressive behaviors have been documented in children with sleep disordered breathing.[25] In addition children have been found to have poorer school performance and perform poorly in measures of attention, vigilance as well as that of executive functioning.[26] Gozal et al have demonstrated that students of grade I in lowest 10th percentile of their class academically had an amazingly high proportion (18%) of home studies suggestive of sleep-disordered breathing, reflecting the effect of sleep-disordered breathing on intellectual function.[27] In type II pediatric OSAS presence of obesity may exacerbate/compound/ alleviate the behavioral disturbances.[28]

Excessive day time sleepiness (EDS) is not as common as adults but it is seen in approximately 13-20 % of children with OSAS using multiple sleep latency test. EDS is more common in type II OSAS as compared to type I. [29, 30] Cardiovascular morbidities have been documented in pediatric OSAS similar to adult OSAS, albeit with reduced severity possibility due to increased compensatory vascular capacitance in children. [16] Higher diastolic pressure in children with OSAS as compared to primary snoring has been reported. [26] C reactive protein, a marker of systemic inflammation is also elevated among children with OSAS. Prevalence of pulmonary hypertension has not been systemically examined in children; however intermittent hypoxia may induce elevation of pulmonary artery pressure and right ventricular dysfunction. [31, 32, 33]

Similar to adults, children with OSAS have sixfold increased risk of metabolic syndrome, though consensus criteria for metabolic syndrome in children are yet to be defined.[34]

Diagnosis

The diagnosis is based on clinical suspicion, history, and physical finding, and confirmation is made by polysomnography (PSG). Upper airway evaluation may also be required in certain cases.

Upper airway evaluation

Endoscopy: In clinical practice, endoscopy of the upper airway is reserved for children with complicated upper airway structure and altered collapsibility.[4]

Table 1: Difference between pediatric and adult sleep apnoea

	Adult sleep apnoea	Pediatric sleep apnoea
Common etiology	obesity	Adenotonsillar hypertrophy
Symptoms a) Excessive daytime sleepiness	Common	Uncommon
b) Neurocognitive deficits	Uncommon	Poor learning and behavioral manifestations are common
c) Psychiatric manifestation	Common	Uncommon
Cardiovascular morbidities and Metabolic syndrome	Common	Uncommon
Diagnosis (AHI*)	AHI above 5/hr	AHI above 1/hr
Treatment	CPAP**	adenotonsillectomy

* AHI- Apnoea hypopnoea index

** CPAP- Continuous positive airway pressure

Pharyngometry: Acoustic pharyngometry, a non invasive method using sound waves to evaluate upper airway cross section area, has been used successfully in adults, but application in children is limited. [35]

Radiographic evaluation: Among all the radiologic techniques [lateral neck radiograph, cephalometrics, fluoroscopy, computerized tomography and magnetic resonance imaging (MRI)] available to measure upper airway anatomy, MRI is preferred because it can also be used for upper airway reconstruction and respiratory dynamics.[36, 37]

Upper airway collapsibility: Starling resistor model which has given insight regarding upper airway collapsibility in adult is applicable even in children. The critical closing pressure (Pcrit) measured by changes in peak inspiratory flow during continuous external application of positive/ negative pressure correlates well with severity of OSAS, higher the pressure more severe is the OSAS.[38]

Polysomnography

Home monitoring: Unattended home studies in children with OSAS have been improving in quality. Limited sleep study with cardiorespiratory channels and 8 hours of video recording have been shown to have results similar to polysomnography.[39, 40] Polysomnography (PSG) has been recommended by an expert consensus panel assigned by the American Academy of Pediatrics (AAP) as the gold standard test for establishing the presence and severity of SDB in children.[5] American Thoracic Society (ATS) guidelines for performing laboratory based PSG include measure of electroencephalograph (EEG) during sleep for sleep staging, arousal and scoring respiratory events. Other measures of arousals like pulse transit time, peripheral arterial tonometry have been tried successfully however EEG is used most frequently.[4]

The previous guidelines laid down in 1996 by ATS have been more recently supplanted by the American Academy of Sleep Medicine for measuring and scoring respiratory events in children.[41] Oronasal thermal sensor is recommended for detection of both apnoea and hypopnoea.[4]

***Definition* (American Academy of Sleep Medicine)**

Obstructive apnoea: An obstructive apnoea is scored when there is a e" 90% drop in signal amplitude of airflow for e" 90% of the entire event, compared with the pre-event baseline amplitude, and events last for at least duration of two breaths with continued inspiratory effort.[42]

Mixed apnoea: Criteria of obstructive apnoea are met without any inspiratory effort.

Central apnoea: If there is absence of inspiratory effort throughout the duration of event and the event lasts for > than 20 seconds or the event is associated with two missed breaths and is associated with an arousal, an awakening, or a e" 3% desaturation with continued inspiratory effort throughout the entire period of decreased airflow.[42]

Hypopnoea: There is a e" 50 % drop in airflow signal amplitude for atleast 90 % of duration of event, the event lasting for atleast two breaths. And the event should be associated with arousal, awakening or e" 3% desaturation.

Respiratory effort related arousal (RERA): When the arousal lasts for atleast two breaths and is associated with reduction in amplitude of airflow by 50% or there is progressive increase in the inspiratory effort during the event on an esophageal pressure sensor.[42] RERA is useful mainly for defining upper airway resistance syndrome.

Hypoventilation: Sleep-related hypoventilation may be scored when >25% of the total sleep time (TST) is spent with a CO_2 >50 mm Hg. Hypoventilation definition is required for detecting central hypoventilation syndromes.

Apnoea hypopnoea index (AHI)/ Respiratory Disturbance index (RDI): On the basis of normative data, an obstructive apnea index of 1 is often chosen as the cutoff for normality. However, while an apnea index of 1 is statistically significant (i.e., at the 97.5th percentile for an asymptomatic, normative population), it is not known what level is clinically significant.[25]

Treatment

Management of sleep apnoea consists of surgery, continuous positive airway pressure (CPAP) therapy, inhaled nasal glucocorticoid or oral appliance depending on the cause. Indications for surgery are not universal. However, most physicians advocate adinotonsillectomy if AHI is above 5/hr.[43, 44, 45] The role of surgery in children with AHI between 1-5 /hr with adeno-tonsillar hypertrophy is controversial. The risk of postoperative complication due to sleep apnoea should to be considered prior to surgery. Also, not all children with adeno-tonsillar hypertrophy who undergo adeno-tonsillectomy for OSAS are cured. Only about 85 % of children respond to the resection.[46, 47, 48, 49] In obese

children and those with severe OSAS the success rate is less than 85%.[50, 51] Long term outcome have shown that the OSAS recurs in a subset of patients particularly with craniofacial abnormality or family history of OSAS.[52, 53] Hence, children with OSAS should also have a maxillomandibular examination preoperatively to assess the need for orthodontic treatment to expand the oral cavity.

Patients should be reevaluated postoperatively to determine whether additional treatment is required.[25] Children in whom adeno-tonsillar resection does not lead to complete resolution of OSAS and in whom the residual severity of OSAS is moderate to severe (AHI>5), CPAP is indicated.[54, 55] CPAP is effective in children, but it is usually used when adeno-tonsillectomy is delayed, contraindicated, or unsuccessful rather than as a primary treatment.[5] CPAP is also useful for children with neurologic problems or craniofacial problems in whom surgery is not appropriate.

Interanasal high potency corticosteroids have shown favorable therapeutic response in children with OSAS and AHI > 5/hr with enlarged adenoids.[56, 57, 58] This is probably because of expression of presence of á and â glucocorticoid receptor in upper airway.[59] Also, increased concentration of inflammatory mediators such as leucotrines is found in children with OSAS.

Oral appliances have been tried in treatment of OSAS in children with some success however long term studies are required to establish the role of oral appliance in pediatric OSAS.[60, 61]

Upper airway resistance syndrome (UARS)

UARS is described as increasingly elevated negative intrathoracic pressure during inspiration that leads to arousal and sleep fragmentation. The exact prevalence of UARS is not known, however the International Classification of Sleep Disorders now lists respiratory event related arousals as a component of the respiratory disturbance index to diagnose OSAS, so future studies of epidemiology of OSAS may well subsume UARS under the single broadened diagnostic category.[3] It was first recognized in *children* in 1982 almost a decade prior to its recognition in adults.[62] The original description concerned children reported frequent snoring, restlessness during sleep, and sweating. Other characteristics more specific to children included a change in appetite, poor performance in school, and problems with behavior.[63] For diagnosis of UARS, the use of esophageal manometry is usually recommended. Though, daytime sequelae of UARS ameliorate after a tonsillectomy and/or an adenoidectomy the exact role of surgery in UARS is not defined.[64]

Central hypoventilation/apnoea

Causes of central hypoventilation/apnoea are:[65]

Primary due to Central/Late Onset Hypoventilation Syndromes

Or

Secondary due to

- Obesity hypoventilation syndrome
- Central hypoventilation associated with brainstem lesions like Arnold–Chiari malformation Type I or II, Trauma, Hemorrhage, Tumor, Congenital anomalies (including Moebius sequence), encephalitis
- Central hypoventilation associated with other neurological syndromes like Autonomic neuropathies and Neurodegenerative syndromes
- Miscellaneous like Drugs, Hyperthermia, Hypothyroidism

Central/ late onset hypoventilation syndromes

Congenital central hypoventilation syndrome (CCHS) is a rare disorder characterised by chronic alveolar hypoventilation may be associated with neurocristopathies, such as Hirchsprung's disease.[66] Late onset central hypoventilation syndrome (LOCHS) is considered by some as synonymous with a distinct clinical entity of late-onset (childhood) CCHS, in association with hypothalamic dysfunction like hyperphagia, hypersomnolence, thermal dysregulation, emotional lability, and endocrinopathies.[67] CCHS & LO-CHS are diagnosed in patients with normal mechanical properties of the lung in the absence of neuromuscular, pulmonary or cardiac disease or an identifiable brain stem lesion. They are characterized by generally adequate ventilation while the patient is awake but hypoventilation with shallow breathing and normal respiratory rates during sleep.[68, 69] Though, LOCHS/CCHS have been considered idiopathic in origin mutation of PHOX2B gene have

been demonstrated in both the diseases.[66,69] Physiological studies have revealed decreased or absent ventilatory chemosensitivity in response to progressive hypoxaemia and hypercapnia. These children do not perceive the challenges of hypoxaemia and hypercarbia; they are likely to swim or exercise farther and longer than their friends without sensing their physiologic compromise, resulting in a fatal hypoxaemia/ hypercarbia.[68, 70] It has been postulated that autonomic dysfunction in cases of CCHS /LO-CHS leads to respiratory and/or cardiovascular manifestation. CCHS/LOCHS patients require lifelong mechanical assisted ventilation as they do not outgrow this disorder. Several ventilatory support options are available for the infants and the children with CCHS/ LO-CHS. Certain patients require ventilatory support only at night while others may require it through out the day. Those requiring support at night can be managed with Bi-level ventilation whereas others who require ventilatory support though out the day would require tracheostomy and home mechanical ventilator support. Instead of home mechanical ventilator diaphragmatic pacing by phrenic nerve stimulation during wakefulness and Bi-level ventilation at night has been tried successfully.[71]

Central apnoea

Central apnoea is usually associated with Prader–Willi syndrome, Arnold–Chiari malformations, due to compression and/or dysplasia of the brainstem.[66] Children with neuromuscular disorders can also have obstructive apnoea in addition to central apnoea/ hypoventilation. The usual cause of central apnoea is often presumed to be immaturity of the respiratory center, with a weak respiratory response to hypercapnia.

Apnea of prematurity

Apnea of prematurity (AOP) is defined as excessive periodic breathing with pathological apnea in a premature infant. Periodic breathing occurs with greater frequency as gestational age decreases and is present in almost all newborns less than 28 weeks gestation.[72] Even though many respiratory pauses in the premature infant are central, evidence suggests that half of all apneas in premature infants are obstructive or mixed in origin due to complex neuromuscular events required to maintain pharyngeal patency.[73, 74, 75] AOP is often highly responsive to continuous positive airway pressure, and supplemental oxygen. Mechanical ventilation may also be required in some patients. Methylxanthines are currently the most widely used medications in the treatment of AOP.[76]

Hypoventilation during sleep due to chronic pulmonary disease

Patients with a low FRC have little functional reserve, and are more likely to desaturate as a result of REM-related intercostal muscle hypotonia, and increased ventilation–perfusion mismatch. Thus, patients with adequate oxygenation during wakefulness may desaturate during sleep, particularly REM sleep.[77, 78] Sleep-related desaturation has been reported in pediatric patients with cystic fibrosis, bronchopulmonary dysplasia, asthma,[79] kyphoscoliosis and muscular dystrophies. Oxygen therapy is usually indicated for chronic lung disease with PaO2 < 55 mm of Hg, whereas non invasive ventilator is advocated for kyphoscoliosis and ventilatory muscle weakness.[65]

Thus, pediatric sleep disordered breathing differs from adult SDB. Diagnosis and treatment is a challenge as manifestations are subtle. Increased awareness of pediatric SDB and its consequences would improve the diagnosis and optimize the management.

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