

Review

Obstructive Sleep Apnea Syndrome in children

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Abstract

Childhood obstructive sleep apnea (OSA) syndrome is an increasingly recognized morbidity affecting 2-5% of children specifically Asian Indian children due to growing urbanization and nutrition transition, obesity and metabolic syndrome. It is associated with metabolic (resistance to insulin-mediated glucose uptake; insulin resistance), cardiovascular (hypertension and cardiac arrhythmias) and neuropsychological disorders. Polysomnography is the gold standard technique for diagnosis of OSA in children. Severity of OSA is assessed by calculating apnea/hypopnea index. Apnea in children is defined as absence of airflow with continued chest wall and abdominal wall movement for duration longer than two breaths. In children, the most common cause of OSA is enlarged tonsils and adenoids. During sleep there is a considerable decrease in muscle tone, which affects the airway and breathing. Some other causes of OSA in children include obesity, tumor, Down syndrome, Pierre-Robin syndrome, cleft palate repairs, receding chin, allergies and anatomical abnormalities. Wide variety of intermediate phenotype and genes are involved in sleep apnea which makes this syndrome genetically complex. Various adipokines and cytokines have a key role in OSA. Some studies have suggested that oxidative stress may also contribute to the development of OSA. Treatment of patients with OSA has typically been focused on the management of associated conditions such as obesity, adenotonsillectomy, hyperlipemia and cardiovascular disease. Different modalities of treatment include weight loss, lifestyle modifications and, continuous positive airway pressure therapy and surgical treatment.

Key words: Asian Indian, Body mass index, inflammation, Insulin resistance; Obstructive sleep apnea syndrome.

INTRODUCTION

Polysomnography (PSG) is the physiologic recording of variables such as brain waves, eye movement, muscle

Abbreviations: BMI: body mass index; NAFLD: nonalcoholic fatty liver disease; OSA: obstructive sleep apnea; REM: rapid eye movement; CPAP: continuous positive airway pressure; T2DM: type 2 diabetes Mellitus Type; OSAS: obstructive sleep apnea syndrome; SDB: sleep-disordered breathing; AHI: apnoea-hypopnoea index; NREM: non-rapid eye movement; BP: blood pressure; TNF- α : tumor necrosis factor; FABP: fatty acid binding protein; MIF: macrophage migration inhibitory factor; CRP: C-reactive protein; NADPH: nicotinamide adenine dinucleotide phosphate; MS: metabolic syndrome.

tone, breathing and heart rhythm during sleep. Over 80 different types of sleep disorders have been identified, with obstructive sleep apnea (OSA) symptoms occurring in one out of every 20 people. Polysomnography is used to diagnose, or rule out, many types of sleep disorders including narcolepsy, idiopathic hypersomnia, periodic limb movement disorder, parasomnias, and sleep apnea.

The Greek word "apnea" literally means "without breath." There are three types of apneas: obstructive, central, and mixed; of the three, obstructive is the most commonest (Guilleminault et al., 1976). Despite the difference in the root cause of each type, in all three, subjects with untreated sleep apnea stop breathing repeatedly during their sleep, sometime hundreds of times during the night and often for a minute or longer and have repeated episodes of hypoxemia.

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Obstructive sleep apnea (OSA) is a common disorder associated with cardiovascular and neuro-psychological disorders (Redline and Young, 1993). OSA has been estimated to affect 3%–7% of adult men, 2%–5% of adult women, (Feng and Chen, 2009; Young et al., 2002; Lumeng and Chervin, 2008) and up to 4% of children (Lumeng and Chervin, 2008; Feng et al., 2012). Although data are sparse, frequency for OSA has been estimated to be 6%–8% in adult population of India (Sharma et al., 2004).

Obesity is a significant risk factor for OSA. The prevalence of childhood obesity has tripled since the early 1980s, and is presently estimated to be 16%. The risk of OSA in obese children is high at 36%, and may exceed 60% if habitual snoring is present. In a previous multi-centeric study, Bhattacharjee et al. (2010) included 500 subjects, half of whom were obese, adenotonsillectomy led to improved clinical symptoms.. Chen et al. (2012) conducted a prospective study of prepubertal children treated with adenotonsillectomy with subsequent normal polysomnography testing. Most obese children with OSA will also have adenotonsillar hypertrophy. In recent years, “metabolic syndrome” has been shown to be an important manifestation of obesity in children. It encompasses a cluster of metabolic and cardiovascular abnormalities such as dyslipidemia, hypertension, insulin resistant, type 2 diabetes mellitus (T2DM) and inflammatory states may play an independent role in the pathophysiology of obstructive sleep apnea syndrome (OSAS) in children (Redline et al., 1999). Studies on various aspects of OSA in children are limited. Adult studies are used to explain various aspects in childhood OSA.

Epidemiology

International scenario

Studies on children and adolescents have shown that the prevalence of sleep-disordered breathing (SDB) was about 2% among normal children (Lumeng and Chervin, 2008; Rosen et al., 2003) and about 2.5–6% among adolescents (table 1). Guilleminault et al. (1981) reported that 10% of children diagnosed with OSAS were obese. Marcus et al. (1998) showed that 46% of unselected obese children undergoing polysomnography had OSAS. Similarly, Kalra et al. (2005) reported that 55% of morbidly obese children undergoing bariatric surgery had evidence of OSAS.

A population-based study (Kalra et al., 2005) involving 399 children between 2 and 18 years of age found that obesity was the most significant risk factor for OSAS. The reason for such a high prevalence of OSAS in obese children compared with the 2% reported in the

general population remains unknown. However, it may be related to a different underlying phenotype distinguishing it from OSAS in non-obese children and an augmented effect on known causative factors resulting from the obese phenotype. Although the prevalence of OSAS in obese children seems to be very high, the true prevalence of this disease in the general obese population cannot be ascertained from the above studies, which were performed on small and selected obese populations. The diagnostic criteria for OSA in children are somewhat different from those in adults. The apnoea–hypopnoea index (AHI) is an index of sleep apnea severity that combines apneas and hypopneas. AHI is the number of apneas and hypopneas per hour. AHI values are typically categorized as 5–15/hr = mild; 15–30/hr = moderate; and > 30/h = severe. Among children, an apnea–hypopnea index (AHI>1) and oxygen desaturation \geq 4% are indicators of mild OSA [17]. In comparison, an AHI of 5 (or sometimes 10) among adults generally indicates mild OSA.

Indian Scenario

According to preliminary reports, OSA affects 3–8% adults in urban population in India (Sharma et al., 2006). As observed in various studies, with growing urbanization and nutrition transition, obesity is increasing in Asian Indians (Misra et al., 2005), which can be a risk factor for OSA in Asian Indians as well. Although these diseases are multi-factorial, genetic associations and hormonal determinants have been suspected and need to be researched in Asian Indians. It is important to investigate these issues in view of large burden of the metabolic syndrome and coronary heart disease in Asian Indian in India and those settled as sizable migrant populations in several countries worldwide. As observed in various studies, with growing urbanization and nutrition transition, obesity, OSA and metabolic syndrome is increasing in Asian Indians (Misra et al., 2005; Agrawal et al., 2011).

Nanaware et al. (2006) studied 56 children's in the study 23(41%) cases were positive for SDB, 12 (52.1 %) patients had craniofacial abnormalities, 4 (17.3%) had neuromuscular and skeletal disorders, 2 (8.6%) had adenotonsillar hypertrophy, 1(4.3%) had bilateral vocal cord palsy and 3 (13%) had sleep apnoea associated with multisystemic disorders. Further, he showed that 41% of suspected cases were detected to have SDB. Jain and Sahni (2002) studied 40 children (age group 4–12 years) with adenoidectomy and tonsillectomy was subjected to pre and post-operative polysomnography. They observed that 75% children presented with predominant obstructive symptoms and 73.3% were found to have OSA. There was a highly significant

Table 1. Prevalence of sleep apnea in children

No. of subjects	Location	Year	Age	Definition of apnea	Prevalence (%)
10,279	Singapore	2004	4–7 yr	Child stops breathing for short periods during sleep (yes/no)	1.2
5,979	China	2005	2–12 yr	Breathing pauses	0.2
3,871	Korea	2003	15–18 yr	Breathing cessation during sleep >43/wk	0.9
3,680	Greece	2004	1–18 yr	Child stops breathing during sleep every	1.0
3,047	Hong Kong	2005	6–12 yr	Child stops breathing for a few seconds or struggles to breathe	1.5
3,045	Belgium	2006	6–13 yr	Child gasps for breath or is unable to breathe during sleep	0.8
2,900	Iran	2006	11–17 yr	Apnea (unclear how defined)	0.4
2,147	Turkey	2004	5–13 yr	Apnea (unclear how defined)	5.6
1,494	United States	2003	4–11 yr	Child stops or struggles to breathe, child's lips turned blue,	3.8
1,014	United States	2000	13–16 yr	Child stops breathing or breathes abnormally every	0.4
895	Italy	2001	3–11 yr	Child has apnea during sleep	2.8
454	Iceland	1995	6 mo–6 yr	Apnea often and very often	1.6
325	Sweden	1995	4 yr	Apnea every night	1.5
245	United Kingdom	1996	0–10 yr	Child appears to hold breath for short periods of time during sleep sometimes or often	4.0
101	Spain	2001	12-16 yr	Witnessed apnea ever	2.9

improvement in polysomnographic scores following surgery in all patients.

Causes

The most common cause of OSA is enlarged tonsils and adenoids. During sleep there is a considerable decrease in muscle tone, which affects the airway and breathing. Infections may cause these glands to enlarge. Large adenoids may completely block the nasal passages and make breathing through the nose difficult. Many of children have little difficulty breathing when awake; however, with decreased muscle tone during sleep, the airway becomes smaller, and the tonsils and adenoids block the airway, making the flow of air more difficult and the work of breathing harder. Obesity may cause obstructive sleep apnea. Some other of the causes of OSA in children include down syndrome, pierre-robin syndrome, cleft palate or cleft palate repairs, receding chin, allergies, anatomical abnormalities (Redline et al., 1999; Rosen et al., 2003; Nanaware et al., 2006; Jain and Sahni, 2002).

Pathophysiology

The etiology of childhood OSA is quite different from that of the adult condition. The upper airway resistance syndrome is characterized by brief, repetitive respiratory effort-related arousals during sleep in the absence of overt apnea, hypoapnea and gas exchange abnormalities (Guilleminault et al., 1993). Also, children with OSA manifest recurrent episodes of partial airway

obstruction. During non-rapid eye movement (NREM) sleep, obstructive events are generally accompanied by an initial decrease in respiratory effort, followed by a graded increase. In REM sleep, the respiratory effort is more variable and may increase or decrease during an obstruction. In addition to adenotonsillar hypertrophy, causes of airway narrowing include allergic rhinitis, turbinate hypertrophy, deviated septum, and maxillary constriction (Guilleminault and Abad, 2004). Figure 1.

OSA and hypertension

The effect of simple snoring on blood pressure (BP) was examined in a study that included children with snoring but without OSA. Kohyama et al. (2003) showed that those with apnea hypoapnea index (AHI) >10 had higher systolic and diastolic BP indexes during REM sleep and during wakefulness compared with those with AHI <10. Another study found that hypertension in 239 Hispanic children from the Tucson Children (Kohyama et al., 2003). Systolic and diastolic hypertension and sleep efficiency were independently associated with respiratory disturbance index. Night time BP may be higher in children with OSA. BP recorded during polysomnography in 41 children with OSA subjects and 26 children with primary snoring showed a significantly higher diastolic BP for sleep and wakefulness in the OSA group (Marcus et al., 2006). On the basis of the current literature, there is no definitive evidence that established hypertension is a common cardiovascular complication of OSA in children and adolescents. It is unlikely that mild OSA in children will lead to significant cardiac dysfunction in the pediatric age range. However,

Pathophysiology

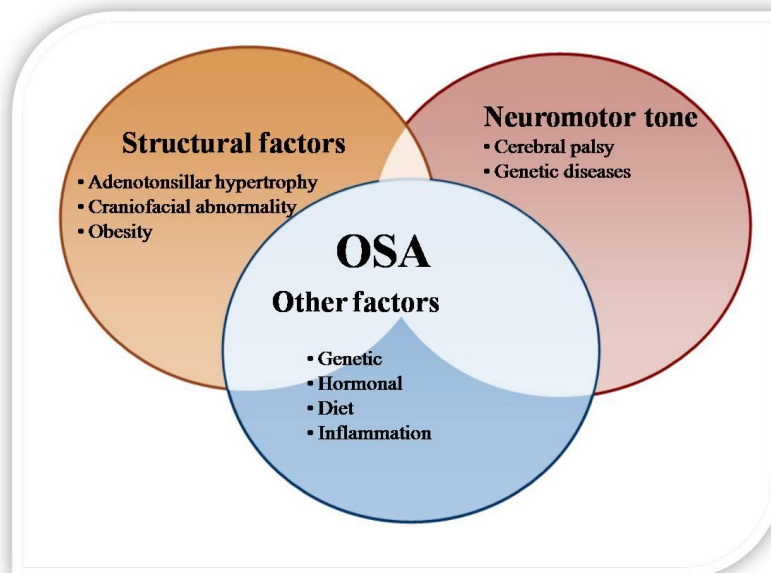


Figure 1. Pathophysiology of OSA

it is not known whether mild OSA during early childhood predisposes to vascular injury or BP dysregulation during adolescence and adulthood. Whether OSA is an independent risk factor for systemic hypertension in children remains unanswered.

Relation between OSA, fat distribution and insulin resistance

There is no consistent relationship between pediatric OSA and measures of body fat distribution (Verhulst et al., 2007). Although imaging studies specific to obese children have not been performed, adult studies indicated that increased deposition of fat in the parapharyngeal fat pads near and within the soft palate contributes to airway obstruction. Obese subjects also have lower lung volumes, increasing both airway compliance and gas exchange abnormalities. Previous study (Verhulst et al., 2009) showed that the relationship between fat distribution and OSA relied on measurements of waist/hip ratios and total body fat and has not found a clear cut relationship between fat distribution and OSA. In children, both visceral adiposity and intramyocellular lipid content, a measure of fat accumulation at the cellular level determined by spectroscopy, has been shown to be a strong predictor of insulin resistance (Weiss et al., 2005).

OSA is associated with insulin resistance, cardiovascular and neuropsychological disorders. It

affects 4-11% of the white Caucasian population. Obesity appears to increase risk of OSA nearly 10–14-folds, with the most marked effects observed in middle-aged subjects (Guilleminault et al., 1976; Redline and Young, 1993). Obesity may increase susceptibility to OSA through fat deposition in upper airway tissues. The co-occurrence of OSA, central obesity, hypertension, and hyperglycaemia suggests that OSA is a part of the metabolic syndrome in adult subjects (Catterall et al., 1984). Despite some evidence, relationship of OSA with insulin resistance independent of obesity remains to be established. In our ongoing investigation on metabolic and genetic factors of OSA, nearly 2/3rd patients with the metabolic syndrome have OSA [unpublished observations]. Clearly, more investigations on the relationship between the metabolic syndrome and OSA are needed in South Asians.

Genetics of OSA

Many studies have been documented showing strong genetic association of OSA (Abdelnaby et al., 2011; Bharat et al., 2011; Khalyfa et al., 2012; Gozal et al., 2012). The list of biologically plausible candidate genes that might be involved in the determination of OSA and associated traits is extensive and growing. There are two kind of approaches used to study genetic association of a disease: whole genome scan analysis and candidate gene approach. Mapping of human susceptible loci for

OSA is difficult due to high population frequency and genetic heterogeneity. Some studies carried out using candidate gene approach have also been documented but no specific conclusion can be drawn from those studies.

Abdelnaby et al. (2011) reported that the presence of symptoms of excessive daytime sleepiness to increased tumor necrosis factor (TNF- α) levels and the TNF- α -308G gene polymorphism. Bhushan et al. (2011) showed that young school-age children with OSA and obesity exhibit higher circulating levels of the pro-inflammatory fatty acid binding protein (FABP)-4. Furthermore, selective variants in FABP4 gene appear to contribute to the proinflammatory or diabetogenic potential of OSA and obesity during childhood. Khalyfa et al. (2012) was studied a total of 614 consecutive children ages 5-8 years. He showed that childhood OSA was associated with higher plasma macrophage migration inhibitory factor (MIF), high-sensitivity C-reactive protein (Hs CRP), and fasting insulin levels that promote cardiometabolic risk, and the MIF gene SNP rs10433310 may be risk factor for OSA. Gozal et al. (2012) reported that the Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase gene may account for important components of the variance in cognitive function deficits associated with OSA in children. Further studies replicating these findings in different populations are needed as are studies involving fine mapping of this region. In Asian Indian, till date no any genetic study of OSA in children has been investigated.

Hormonal studies in OSA

Most of the documented hormonal studies have been carried out mainly taking acromegaly as an intermediate in OSA. Hormonal levels also have been found to be strongly associated with sleep. Disturbed sleep wake behavior by sleep deprivation results in changes in hormone secretion. Studies carried out individually in OSA have been done in small number of subjects (Meyer et al., 2012; O'donnell et al., 1999) but no study has been reported in Indian context.

Treatment

Treatment of patients with OSA has typically been focused on the management of associated conditions such as obesity, Adenotonsillectomy, hyperlipemia and cardiovascular disease (Capdevila et al., 2008). Weight loss has been shown to improve insulin sensitivity, and OSA may resolve with weight reduction. Insulin resistance seems to be the common denominator in

many cases of OSA. Different modalities of treatment have been advocated for the management of OSA. These include lifestyle modifications and weight reduction, CPAP therapy and surgical treatment.

Surgical

Adenotonsillectomy (T & A) is generally considered to be the standard treatment of childhood OSA with normal craniofacial features and uncomplicated medical status. In a meta-analysis of the published literature, the success rate in the context of OSA was observed to be approximately 85% (Lipton and Gozal, 2003). This data may actually be lower, particularly among obese children with OSA or among children with severe OSA (Shine et al., 2006). However, another study has suggested that cure is achieved in less than 50% with persistent SDB occurring because of other facial structural issues such as retrognathia, enlarged nasal turbinates and a deviated septum. A study from India, Paramasivan (2012) studied 50 cases of children with OSA age group between 5 and 12 years were randomly selected for each group and studied. He concluded that the use of coblation for adenotonsillectomy may have several advantages over standard methods for the treatment of children with OSA. It is highly efficacious, practical and safe with less morbidity and less complications.

Life style modifications and weight reduction

Weight gain is a significant risk factor for the development of OSA. In the vast majority of OSA cases the illness can be improved, if not eliminated, with significant weight loss. However anatomic abnormalities may cause the condition to persist. The amount of weight a patient needs to lose to achieve these benefits varies. Some may need only a modest reduction in weight to gain improvement, while others may require significant weight loss. It is usually not necessary to slim down to an "ideal body weight" to achieve these benefits. The theoretical advantages of weight loss include decreasing insulin resistance and, if combined with exercise, increasing muscle insulin sensitivity. Weight reduction has been clearly associated with improvement in liver biochemical tests. One study indicated that in obese children, weight loss and maintaining a healthy diet might prove to be the ultimate treatment for their OSA (Benninger and Walner, 2007). A recent study in adolescents showed that 72 percent (13 out of 21) overweight children with sleep disorder breathing were able to reduce their AHI to <2 with weight loss (Verhulst et al., 2007).

Continuous positive airway pressure therapy (CPAP)

CPAP is an effective therapy for OSA. It is useful for children who are unable to have T&A or who have residual SDB post operatively. The CPAP machine sends air under pressure through the tube into the mask, where it imparts positive pressure to the upper airways. This essentially acts as "splints" and keeps the upper airways open and prevents them from collapsing. CPAP is the most commonly prescribed treatment for OSA. The advantages of CPAP are that it is safe and completely reversible and is generally quite well tolerated. Ghoshal et al. (2010) showed that the treatment with CPAP was effective in 68.23% cases in first attempt. More than half of the cases (62.42%) required 10 cm of H₂O or less CPAP. Another study indicated that CPAP has been found to be effective for the treatment of OSA in children (McNamara and Sullivan, 1999).

CONCLUSION

Obesity is associated with OSA in children. Importantly, several epidemiologic studies have demonstrated that sleep related disorders are an independent risk factor for obesity and hypertension, probably resulting from a combination of intermittent hypoxia and hypercapnia, arousals, increased sympathetic activity, and altered baroreflex control during sleep.

Obesity and MS are increasing in Asian Indians. Although these diseases are multifactorial, genetic associations and hormonal determinants have been suspected but not researched. It is important to investigate these issues in view of large burden of insulin resistance and metabolic syndrome in Asian Indian children. We feel that strongly support a relationship between OSA. Further studies are needed to elucidate the precise nature of this relationship.

The genetic and hormonal determinants of OSA have received little attention. Wide variety of intermediate phenotype and genes are involved in sleep apnea which makes this syndrome genetically complex. In a linkage analysis study, genes associated with obesity were shown to be relevant for further study of OSA.

Lifestyle intervention should be first line treatment for OSA patients. In identifying and treating OSA among children with adenotonsillar hypertrophy, dentists can play an important role by noting the size of the tonsils when looking into child's mouth and informing the child's parents and the primary care physician when enlarged tonsils are observed. There is currently no well established treatment for patient with OSA.

Author's contribution

Surya Prakash Bhatt, wrote and edited the manuscript; Randeep Guleria, overall clinical supervision, contributed to the discussion and reviewed/edited the manuscript; Sushil Kumar Kabra, reviewed/edited the manuscript.

Conflict of Interest

None of the authors of the above manuscript has declared any conflict of interest.

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