Published in final edited form as:
Sleep Med Clin. 2007 September ; 2(3): 433–444.

Childhood Obstructive Sleep Apnea: One or Two Distinct Disease Entities?

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Abstract

The spectrum of sleep disordered breathing (SDB) encompasses habitual snoring at the low end of severity all the way to frank obstructive sleep apnea (OSA), with upper airway resistance syndrome (UARS) and obstructive alveolar hypoventilation being considered as less severe variants of this condition. SDB occurs in children of all ages, from neonates to adolescents, and is characterized by repeated events of increased upper airway resistance as well as with either partial or complete upper airway obstruction during sleep, all of which may result in disruption of normal gas exchange and sleep integrity [1]. SDB was initially described over a century ago [2] and was then rediscovered in children by Guilleminault in 1976 [3]. However, this complex and relatively prevalent disorder is only now being recognized as a major public health problem. During the initial years since the seminal paper by Guilleminault et al [3], it became apparent that the classic clinical syndrome of OSA in children markedly differed from the OSA seen in adults, in particular with respect to gender distribution, clinical manifestations, polysomnographic findings, and treatment approaches [4,5]. However in more recent years, the epidemic of obesity that affects the pediatric population all over the world has led, in our opinion, to the emergence of a phenotypic variant of OSA in children that closely resembles that of adults with the disease. In this paper, we will review the pathophysiological mechanisms of OSA in children, delineate the clinical manifestations associated with the disease, and provide arguments for our novel and hopefully useful proposition that aims to define 2 types of OSA in children. For the sake of convenience, and in analogy with type I and type II diabetes, we propose to divide pediatric OSA as types I and II.

Keywords

obstructive sleep apnea; adenotonsillar hypertrophy; obesity; inflammation; upper airway; snoring

Epidemiology of Pediatric OSA

Habitual snoring during sleep, the hallmark indicator of increased upper airway resistance, is an extremely frequent occurrence during childhood, with up to 27% of children being affected [6–14]. SDB is most common in young children (pre-school and early school years), with a peak prevalence around 2–8 years, and subsequent declines in frequency [15]. However, accurate prevalence information is missing, particularly in infants, since most epidemiological studies have to date concentrated on older children. Furthermore, the exact polygraphic

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demarcation between the presence of habitual snoring that does not entail any adverse consequences (if such entity indeed exists), and that associated with morbid consequences is probably unrealistic, considering the large inter-individual variability in clinical phenotypic presentations. Thus, a consensus statement was generated [16], and based on such criteria, it is currently estimated that of the many children with habitual snoring, approximately 2–3% will have clinically-relevant OSA [17]. Therefore, the ratios between habitual snoring and OSA vary from 4:1 to 6:1.

In recent years, the epidemic increase in obesity prevalence during childhood appears to be contributing to substantial changes in the cross sectional demographic and anthropometric characteristics of the children being referred for evaluation of SDB. Indeed, while <15% of all symptomatic habitually-snoring children were obese (i.e. >95% for age and gender) in the early 90's, >50% fulfilled the criteria for obesity among all referrals for suspected SDB in the last 2 years at our Sleep Center [18]. Considering that obesity can clearly play a role in the pathophysiology of upper airway obstruction during sleep (see below), it is likely that the ratio between habitual snorers and those with clinically relevant OSA among obese children may differ from the ratios reported for non-obese children [19].

Unfortunately, extensive clinical history and thorough physical examination are unreliable predictors of disease [20], accurate screening tools are not presently available, and as such, overnight polygraphic recordings remain the only validated diagnostic approach for both non-obese and obese snoring children.

Classification of OSA Severity Categories

While the severity spectrum of SDB is probably best viewed as a continuum, it is probably helpful to divide this heterogeneous group into severity based categories. As a cautionary preamble, the criteria proposed herein for such classification have not been validated by appropriate scientific methodology, but have rather evolved from our empirical experience in the management of several thousands of habitually snoring children over 2 decades.

Before addressing this issue, we should point out that several studies on normative polysomnographic data in children have been recently published [21–25]. Table 1 shows proposed criteria for the various severity-related entities as they are currently used in our sleep center. In addition, Figures 1–4, provide examples of events as they are routinely recognized in the polysomnographic assessments conducted in children.

Pathophysiology of OSA: Tonsils/Adenoids vs. Obesity

OSA occurs when the upper airway collapses or at least significantly reduces its luminal cross sectional area during inspiration. Such dynamic process involves interactions between sleep state, pressure-flow airway mechanics, and respiratory drive. When resistance to inspiratory flow increases or when activation of the pharyngeal dilator muscle decreases, negative inspiratory pressure may promote the collapsibility of the upper airway [26]. Both functional and anatomic factors may tilt the balance toward airway collapse. Indeed, it has been determined that the site of upper airway closure in children with OSA is at the level of the tonsils and adenoids, whereas in normal children it occurs at the level of the soft palate [27].

The size of the tonsils and adenoids increases from birth to approximately 12 years of age, with the greatest increase taking place during the first few years of life, albeit proportionately to the growth of other upper airway structures [28] However, lymphadenoid tissue will especially proliferate in children exposed to environmental irritants, such as cigarette smoke [29,30]. Additionally, the presence of allergic rhinitis [31,32], and asthma [33] have been implicated in increased prevalence of adenotonsillar hypertrophy and OSA. More recently, a potential link

between viral respiratory infections during infancy and the proliferative properties of upper airway lymaphadenoid tissues has emerged, whereby early viral infections may predispose for increased risk of adenotonsillar hypertrophy [34]. Genetic factors also may play a role in the pathophysiology of OSA, as demonstrated by studies of family cohorts [35,36]. It is unclear whether this is due to the modulating influence of genetic factors on ventilatory drive, anatomic features, or both. Ethnicity is also important, with OSA occurring more commonly in African Americans [37].

Interestingly, several studies have failed to show a strong correlation between upper airway adenotonsillar size and OSA [38–42]. We now propose that such discrepant findings may be explained by the varying proportion of obese children included in each of these studies. Indeed, similar to adults, obese children are at increased risk for developing sleep-disordered breathing, and the severity of OSA is proportional to the degree of obesity [43–46], such that for every increment in BMI by 1 kg/m^2 beyond the mean BMI for age and gender, the risk of OSA will increase by 12%. Conversely, adenotonsillar hyperplasia/hypertrophy is not always the main contributing factor to the development of OSA in obese children (47–49]. In fact, interactions between these 2 factors, namely BMI and tonsil/adenoid size have been independently implicated in the risk for OSA [50]. Upper airway narrowing in obesity will result from fatty infiltration of upper airway structures, while subcutaneous fat deposits in the anterior neck region and other cervical structures will also exert collapsing forces promoting increased pharyngeal collapsibility [51–53]. Moreover, obesity can affect ventilation through mass loading of the respiratory system [54], while increased adipose tissue in the abdominal wall and cavity as well as surrounding the thorax increases the global respiratory load, and reduces intrathoracic volume and diaphragm excursion, particularly in the supine position [55]. Taken together and based on the relative pathophysiological contributions that can be ascribed to adenotonsillar hypertrophy and upper airway fat deposition in the generation of OSA, we propose that 2 types of OSA disease exist, namely one associated with marked lymphadenoid hypertrophy in the absence of obesity (type I) and the other being primarily associated with obesity in the presence of only mild lymphadenoid hyperplasia (type II). While significant overlap undoubtedly exists between these 2 entities, this conceptual framework may further facilitate the distinction between patients and provide improved formulation of therapeutic interventions. As a corollary, we have recently reported on the high failure rates of adenotonsillectomy in obese children [56].

Clinical Presentation and Morbidity of OSA in Children

The clinical presentation of a child with OSA is usually vague and requires increased awareness of the primary care physician. In Table 2, we present some of the similarities and differences between type I and type II pediatric OSA. We should also emphasize that the implications of OSA in children, are quite broad in scope and rather complex. If left untreated, or alternatively if treated late, pediatric OSA may lead to substantial morbidity that affects multiple target organs and systems, and such morbidity may not be completely reversible with appropriate treatment. OSA in children can lead to behavioral disturbances and learning deficits, cardiovascular morbidity, metabolic disturbances, and compromised somatic growth as well as decreased quality of life and depression. However, not all children with OSA will manifest such consequences, and therefore it is reasonable to assume that in addition to the severity of the underlying OSA, genetic and environmental factors must play a critical role in determining the susceptibility to end-organ injury [57]. In this context, the presence of obesity will, in our opinion, modify the susceptibility to OSA and dictate some of the differences in phenotypic manifestations. Table 2 shows some of the major similarities and differences in the clinical presentation of type I and type II OSA in children.

Neurobehavioral Consequences

Behavioral and neurocognitive dysfunction are now well-characterized consequences of OSA in children. Schooling problems have been repeatedly reported in case series of children with OSA, and in fact may underlie more extensive behavioral disturbances such as restlessness, inattention, aggressive behavior, excessive daytime sleepiness and poor schooling [58–63]. In fact, rather compelling and substantive evidence has accumulated in recent years to support causative associations between OSA and hyperactivity and inattentive behaviors as well as cognitive deficits [64–71] In addition, parentally-reported daytime sleepiness, hyperactivity, and aggressive behaviors have all been documented in children who snore, even in the absence of OSA [72–75]. However, excessive daytime sleepiness as measured by multiple sleep latency tests is relatively infrequent in pediatric OSA (type I), except when obesity is present (type II) [76].

The exact mechanisms by which OSA elicits such neural deficits remain relatively unresolved. Most likely, both the sleep fragmentation and episodic hypoxia that characterize OSA lead to alterations within the neurochemical substrate of the prefrontal cortex with resultant executive dysfunction [77–79], and may also elicit neuronal cell losses [80,81].

We would also propose that the manifestations of excessive daytime sleepiness may differ in children with type I OSA compared to either children with type II OSA or adults, such that in type I, both inattention and hyperactivity constitute behavioral correlates of sleepiness. Indeed, when we examined the magnitude of sleep fragmentation induced by OSA in children, a numerical score derived from the arousal indices and denominated as the sleep pressure score, correlated with both cognitive and behavioral disturbances occurring in snoring children, independent from the degree of hypoxemia [82,83].

Notwithstanding, improved learning and behavior will occur after treatment in type I OSA children [84–88], thereby suggesting that the neurocognitive and behavioral deficits are at least partially reversible [89].

The susceptibility to OSA-induced cognitive deficits and the reversibility of such deficits upon treatment may not be as favorable in type II OSA. Since type II OSA children are much more likely to be either overweight or obese (similar to adults), we should keep in mind that overweight children will be more likely to display significantly lower math and reading scores compared to non-overweight children, and to be held back in grade [90,91], thereby making predisposing them to unfavorable interactions with OSA. Moreover, IQ and performance IQ of obese children were significantly lower compared to normal weight children in a study in China [92], and an increased prevalence of behavioral and learning difficulties has been observed among children who are gaining weight rapidly [93]. While obesity could be a marker rather than represent a cause of low academic performance [90], it is important to emphasize that both obesity and OSA are systemic inflammatory diseases [94–96]. The interaction between the 2 inflammatory cascades linked to OSA and obesity could potentiate the morbid effects of these 2 conditions, and therefore account for the different manifestations described in type II OSA (Table 2). Preliminary evidence in support of such hypothesis has been recently presented, and further supports the validity of categorical differentiation of pediatric OSA sub-types [97,98].

Cardiovascular Consequences

Pediatric OSA has been now associated with a higher risk for cardiovascular morbidities. For example, increased prevalence of altered blood pressure regulation [99], systemic hypertension [100–102], and changes in left ventricular geometry [103,104], have all now been reported in children with OSA. The underlying mechanisms mediating such findings are most likely linked

to the underlying increases in sympathetic activity and reactivity [105–107], as well as altered endothelial function [108]. Parenthetically, the endothelial dysfunction associated with OSA is most likely the result of initiation and propagation of inflammatory responses within the microvasculature [109]. Consequently, it was anticipated and since then it has been further confirmed that similar to adults, plasma concentrations of C-reactive protein, an important circulating marker of inflammation, are elevated in a severity-dependent fashion among children and adolescents with OSA, even after correction for body mass index [110–112]. Just as a reminder, the intermittent hypoxia during sleep that occurs in children with OSA may result in sustained elevations of pulmonary artery pressures and potentially lead to *cor pulmonale* [113,114]

Quality Of Life and Depression

There is little doubt that both OSA and obesity lead to significant decreases in quality of life in children [115–120]. Conversely, quality of life will improve following treatment of OSA [121]. Based on preliminary and unpublished data, obese children with OSA (type II) are significantly more likely to present with reduced quality of life when compared with non-obese children (type I) (Odds Ratio: 1.78; Confidence Intervals: 0.71–4.55; $p<0.02$; n=100 patients, namely, 38 with type I and 62 with type II OSA). It is likely that the sleep disturbance associated with OSA will increase fatigue, lead to increased irritability, depressed mood, impaired concentration and decreased interest in daily activities. These impairments in daily functioning may in turn interfere with other aspects of the child's life, including relationships with family, school, and peers.

Insulin resistance, Type 2 Diabetes and Metabolic Syndrome

The term "metabolic syndrome", a known risk factor for cardiovascular disease in adults, refers to the clustering of insulin resistance, dyslipidemia, hypertension, and obesity. While the criteria for the metabolic syndrome are still unclear in the pediatric age range [122], Weiss and colleagues found that the risk of the metabolic syndrome was nearly 50% in severely obese youngsters and risk increased with every 0.5 unit increment in BMI (converted to a Z score) [123], with elevated fasting insulin levels and increased body mass index (BMI) during childhood emerging as the strongest predictors of the metabolic syndrome in adulthood [124, 125].

Similar to obesity, OSA has been identified as an important risk factor for the metabolic syndrome in adult patients [126–128]. In children, both insulin resistance (measured by Ins/Glucose ratio and HOMA (homeostatic model assessment) and altered lipidemia (evidence of increased plasma TG and decreased plasma HDL concentrations) are primarily determined by obesity and are very minimally affected by OSA [129,130 However similar to adults, when obesity and OSA coincided in children (type II), there was evidence of interaction between these 2 conditions to induce metabolic disturbances [131132.

Somatic Growth Impairment

For the sake of completeness, we should include the fact that somatic growth impairments can be a consequence of OSA in children. Indeed, failure to thrive (FTT) used to be one of the common sequelae of childhood OSA [133–135]. However, the frequency of this problem has markedly diminished in recent years. Interestingly, even obese children with OSA will demonstrate accelerated weight gain after treatment of the underlying OSA [136,137].

Suggested mechanisms for somatic growth alterations in OSA include decreased appetite, dysphagia due to tonsillar hypertrophy, and decreased levels of insulin growth factor -1 (IGF-1), IGF binding proteins, and possibly growth hormone release [138,139].

Summary

The increasing prevalence of obesity in children has revealed a clinical picture of OSA that is markedly reminiscent of the typical presentation of OSA in adult patients, and that remarkably differs from the original presentation and manifestations of OSA in children. This “newer” adult-like” entity accounts nowadays for almost 50% of all cases seen in pediatric sleep clinics. As such, the dichotomous clinical features of these 2 subtypes of pediatric OSA are further described in detail. We further suggest that use of this classification may allow for improved delineation of management strategies, and help define potential disparities in short-term and long-term clinical outcomes.

Acknowledgements

Funding Sources: This study was supported by NIH grant HL-65270, The Children’s Foundation Endowment for Sleep Research, and by the Commonwealth of Kentucky Challenge for Excellence Trust Fund.

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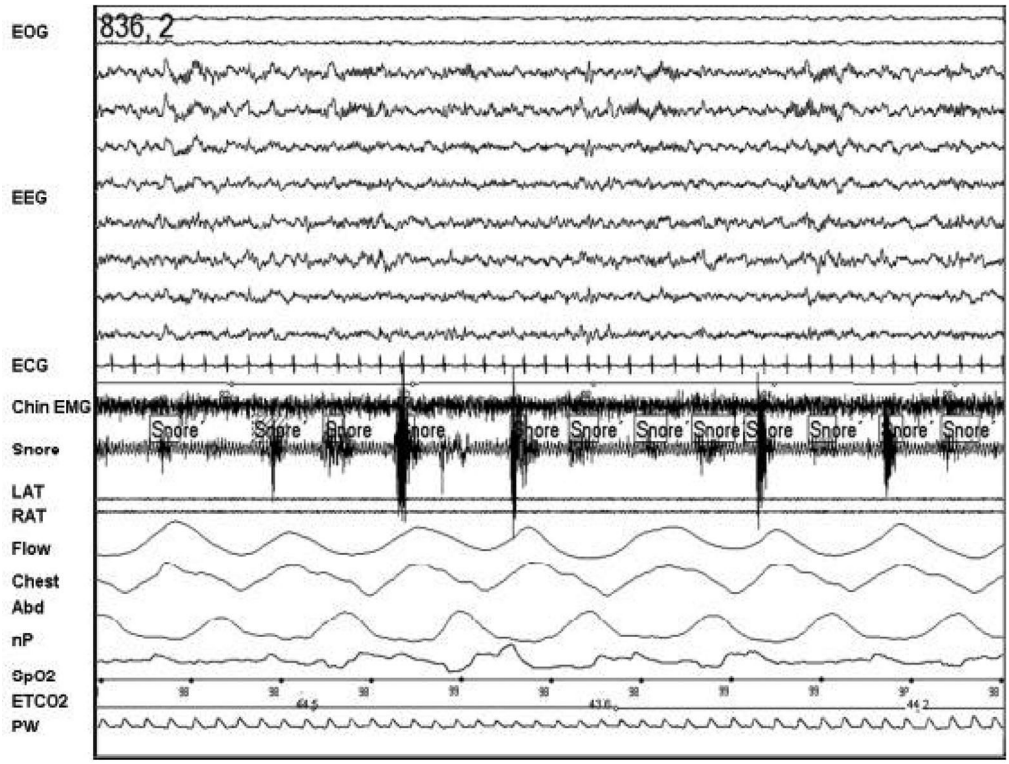

Figure 1. Habitual snoring in a 4-year old child without any evidence of gas exchange abnormalities or sleep alterations

EOG-electrooculogram; EEG – electroencephalogram; ECG – electrocardiogram; chin EMG – chin electromyograms; Snore – sound channel; LAT – left anterior tibial EMG; RAT – right anterior tibial EMG; Flow – thermistor derived oronasal flow; Chest – chest respiratory excursion; Abd – abdominal respiratory excursion; nP – nasal pressure; SpO2- oxyhemoglobin saturation by pulse oximetry; ETCO2 – end tidal carbon dioxide; PW- pulse waveform from pulse oximeter

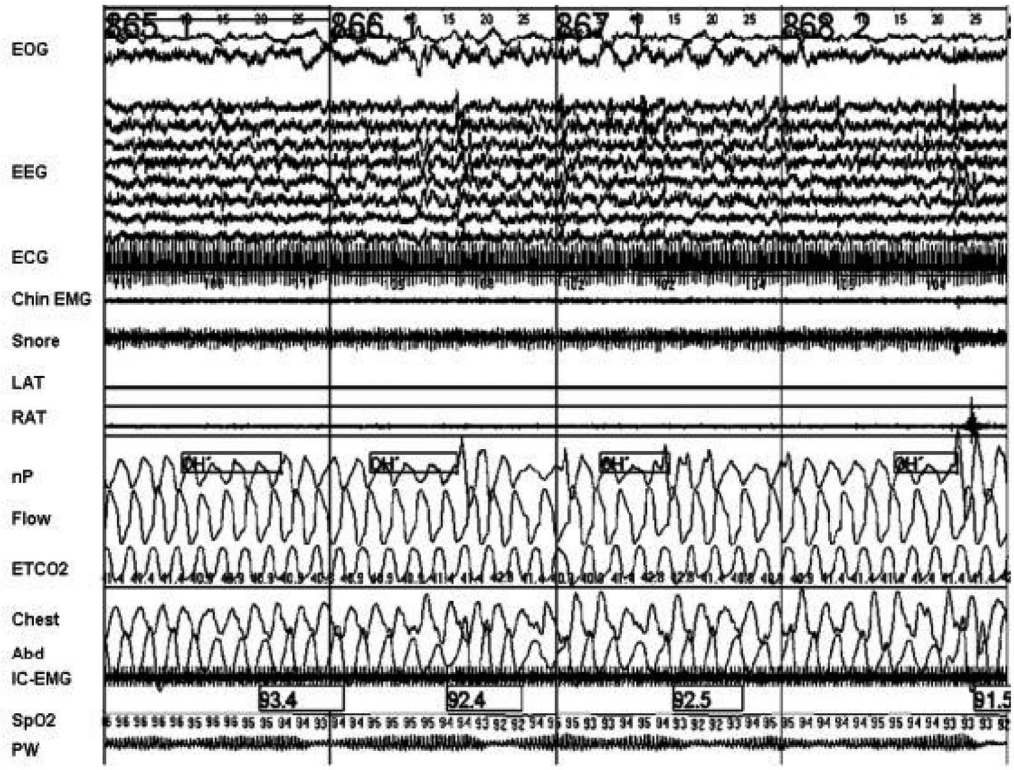

Figure 2. Polygraphic tracing in a 7-year old child with upper airway resistance

EOG- electrooculogram; EEG – electroencephalogram; ECG – electrocardiogram; chin EMG – chin electromyograms; Snore – sound channel; LAT – left anterior tibial EMG; RAT – right anterior tibial EMG; nP – nasal pressure; Flow – thermistor derived oronasal flow; ETCO2 – end tidal carbon dioxide; Chest – chest respiratory excursion; Abd – abdominal respiratory excursion; IC-EMG – intercostal EMG; SpO2- oxyhemoglobin saturation by pulse oximetry; PW- pulse waveform from pulse oximeter

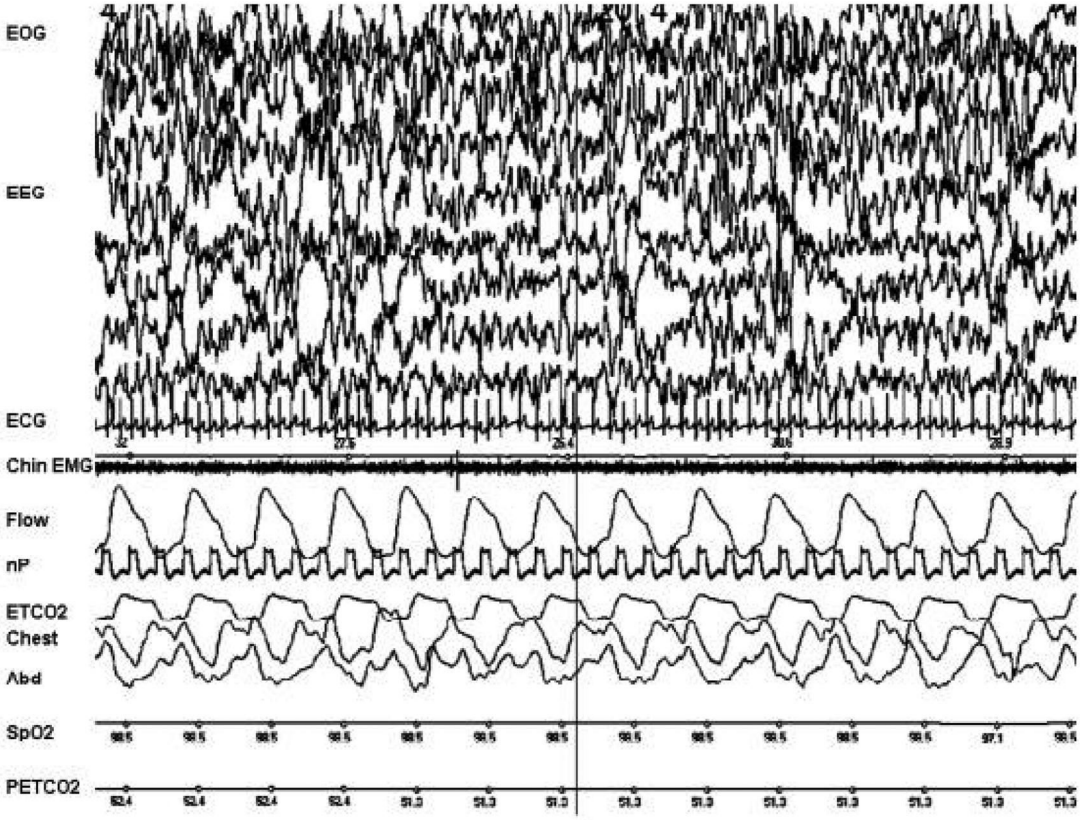

Figure 3. Obstructive alveolar hypoventilation in a 8-year old obese child

EOG-electrooculogram; EEG – electroencephalogram; ECG – electrocardiogram; chin EMG – chin electromyograms;; Flow – thermistor derived oronasal flow; nP – nasal pressure; ETCO2 – end tidal carbon dioxide; Chest – chest respiratory excursion; Abd – abdominal respiratory excursion; SpO2- oxyhemoglobin saturation by pulse oximetry; PETCO2 – end-tidal carbon dioxide readings

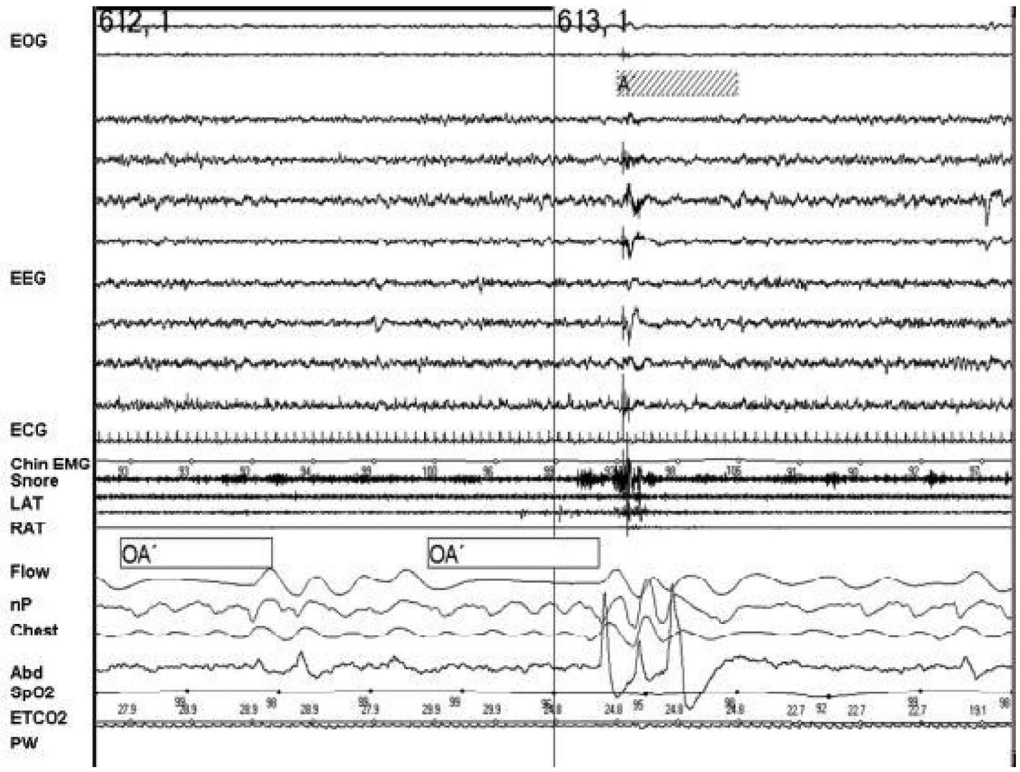

Figure 4. Obstructive sleep apnea in a 3 year-old child

EOG- electrooculogram; EEG – electroencephalogram; ECG – electrocardiogram; chin EMG – chin electromyograms; Snore – sound channel; LAT – left anterior tibial EMG; RAT – right anterior tibial EMG; Flow – thermistor derived oronasal flow; nP – nasal pressure; Chest – chest respiratory excursion; Abd – abdominal respiratory excursion; SpO2- oxyhemoglobin saturation by pulse oximetry; ETCO2 – end tidal carbon dioxide; PW- pulse waveform from pulse oximeter

Table 1

Proposed classification and criteria severity of pediatric sleep disordered breathing.

		OAHI (/hrTST)	Nadir SpO_2 (%)	$P_{ET}CO_2$>50 mmHg (%TST)	RAI (/hrTST)
Normal		= 1	> 94	<10	< 1
Habitual Snoring		= 1	> 94	<10	< 2
Upper Airway Resistance Syndrome		= 2	> 92	10–15	= 2
Obstructive Alveolar Hypoventilation		= 2	> 92	>20	= 2
OSA	**Mild**	2–5	88–92	10–15	2–5
	Moderate	5–10	80–88	15–20	5–8
	Severe	> 10	< 80	>20	> 8

OAHI – obstructive apnea-hypopnea index; PETCO2 – end-tidal carbon dioxide; RAI – respiratory arousal index; TST – total sleep time

Table 2

Clinical Presentation of Pediatric OSA types I and II.

SIMILARLY FREQUENT SYMPTOMS AND FINDINGS SNORING DIFFICULTY BREATHING DURING SLEEP WITH SNORTING EPISODES RESTLESS SLEEP AND FREQUENT AWAKENINGS EXCESSIVE SWEATING NIGHT TERRORS ENURESIS BREATHING PAUSES REPORTED BY PARENTS MOUTH BREATHING AND LIMITED NASAL AIRFLOW CHRONIC RHINORRHEA FREQUENT VISITS TO PRIMARY CARE PHYSICIAN FOR RESPIRATORY-RELATED SYMPTOMS RETROGNATHIA PULMONARY HYPERTENSION AND COR PULMONALE		
	Type I	**Type II**
Excessive daytime sleepiness	+	++++
Weight gain	−	++
Hyperactive behavior	++++	− **or** +
Truncal obesity	− **or** +	+++
Enlarged neck circumference	− **or** +	+++
Enlarged Tonsils/Adenoids	++++	++
Depression and low self-esteem	+	+++
Shyness and social withdrawal	+	+++
Left ventricular hypertrophy	++	++++
Systemic hypertension	+	++++
Recurrent ear infections	+++	− or +
Insulin Resistance	−	++++
Dyslipidemia	+	++++
Elevated C-Reactive Protein	++	++++
Elevated Liver Enzymes	−	++

− : absent

- + infrequent to ++++ - very frequent