THE PUBLISHING HOUSE
OF THE ROMANIANACADEMY

Supplement 1/2015, 4th ISAA

OBESITY AND OBSTRUCTIVE SLEEP APNEA IN CHILDREN

Sorina CHINDRIS[1], Alexandra AVRAMUTA[2] and Doina-Anca PLESCA[1,3]

[1] *"Carol Davila"* University of Medicine and Pharmacy, Faculty of Medicine, Bucharest, Romania
[2] Queen Alexandra NHS Hospital, Trust Grade Doctor, Portsmouth, United Kingdom
[3] *"Victor Gomoiu"* Children's Hospital, Paediatric and Neurologic Department, Bucharest, Romania
Corresponding author: Sorina CHINDRIS, E-mail: sorina@chindris.com

Accepted November 19, 2015

Obesity and Obstructive Sleep Apnea (OSA) are two entities with a high distribution amongst the pediatric population. Obesity and OSA interact and the sum of their side effects determine variable organic reactions. The mechanisms by which obesity and OSA interact are not fully understood at present but this paper tries to summarize some of the most important theories regarding the obesity-OSA correlation. From a pathophysiological point of view OSA can appear secondary to adenotonsillar hypertrophy, craniofacial abnormalities, affected respiratory muscle mechanics or due to metabolic modifications in correlation with obesity. This association determines specific clinical findings and cardiovascular, neurobehavioural and metabolic complications. The link between OSA and obesity in children has also strong genetic bases. Various cytokines and adipokines play an important role for the presence of OSA in obese children. The evaluation of obese children with OSA needs a multidisciplinary team approach in view of forming a correct diagnostic and implementing a treatment therapy. Polisomnography is the gold-standard investigation for OSA and adenotonsillectomy is the first-line treatment for obese children with OSA and adenotonsillar hypertrophy. The earlier a child receives treatment, the higher it is his chance towards a healthy adult life, premise for economic and academic success.

Keywords: child, sleep-related breathing disorders, obstructive sleep apnea, obesity, snoring

INTRODUCTION

Snoring is a common symptom in the paediatric population, occurring in children of all ages but being more commonly seen in preschool-aged children (10%)[1].
Snoring is an annoying noise of variable intensity, produced during breathing and while sleeping, secondary to partial obstruction of the upper airways. As a consequence of this restricted airflow, vibrations appear within the upper airway's soft tissue and this can lead to sleep-related breathing disorders[2].
Sleep-related breathing disorders (SDB) refer to a large spectrum of pathophysiologic entities that appear secondary to partial or total obstruction of the upper airways from primary snoring to upper airway resistance syndrome and obstructive sleep apnea[2].
Obstructive sleep apnea (OSA) is defined by 20% airflow reduction with a minimum duration of 3 seconds or 2 breaths and it is associated with various respiratory effort[2]. OSA is classified depending on severity as mild, moderate and severe[2]. Snoring is an important symptom of SDB but it is not predictive for the presence of OSA[3]. There are children who snore but they do not have OSA. These children can present 1 apnea event/hour and the apnea: hipopnea index is below 1.2 events/hour[2].
OSA was clinically defined and evaluated in the paediatric population around 1970[4,5]. Nowadays, researches in this field try to establish a connection between a child's daily behaviour and sleep-related breathing disorders due to snoring.
Morphological changes secondary to snoring, even in the absence of abnormal arterial blood gases or sleep deprivation, can be associated with high risk of neurobehavioral pathology, cardiovascular morbidity, obesity or growth restriction[2,6].
On and off sleep and intermittent hypoxia determine variable organic reactions with an increasing oxidative stress and systemic inflammatory response[6]. All of these emerge to increase morbidity and mortality amongst children[6].

Epidemiology of OSA in obese children

The prevalence of OSA in obese children varies from 13 to 59% [7]. Habitual snoring incidence in children is 5-7% and it is two times higher amongst obese children[8,9]. In 2012, the American Society of Pediatrics did a meta-analysis of 11 studies on the relation between obesity and OSA and found out that the prevalence of OSA in obese children is four times higher than in nonobese children[10]. This meta-analysis shows that an increase of the body mass index with 1kg/m^2 to median body mass index for age and sex increases the risk of OSA with 12% [11].

The presence of OSA is observed in 46% to 59% of obese children[12]. Marcus CL et al. in 1996 reports that 46% amongst obese children underdoing polysomnography have OSA[13] and Silvestri JM et al. in 1993 points out that 59% amongst obese children presenting with SDB have OSA[14].

The study conducted by Verhulst SL et al. in 2009 shows that waist circumference in obese children is directly proportional with the risk of developing central sleep apnea [15].

Pathophysiology of snoring in children

Pathophysiology mechanisms of snoring are not yet completely defined. There are at least 4 causes related to OSA in children that have been identified [3]:

- *Adenotonsillar hypertrophy* - is the most frequent cause of snoring in children; adenoidal and tonsillar hypertrophy can produce upper airways collaps and various airflow restriction [4,16].
- *Craniofacial anatomy* - craniofacial malformations or craniofacial dysmorphism represents another frequent cause of OSA in children[3]. Craniofacial abnormalities are described as birth defects and airflow restriction becomes more and more important with the increasing size of the abnormal craniofacial bones as well as with the modified bone structure[4].
- *Affected respiratory muscle mechanics* linked to neuromuscular disease, genetic disease or metabolic disease can be another cause that can determine snoring in children. The lack of support in respiratory effort due to muscular atrophy and the difficult thorax distension can determine hypoxia, hypoventilation and different degrees of obstruction in the upper airways[4,17,18].
- *Obesity* in the pediatric population is recognized as an important cause that can determine OSA[19]. Obese children represent a subgroup at risk for OSA and this requires special consideration[4] due to the clinical and metabolic consequences that obesity has upon the human body, consequences that are emphasized by the presence of OSA.

Genes implications in OSA and obesity

Nowadays, we know that both OSA and obesity are genetically coded, modeling each individual phenotype (figure 1) [21].

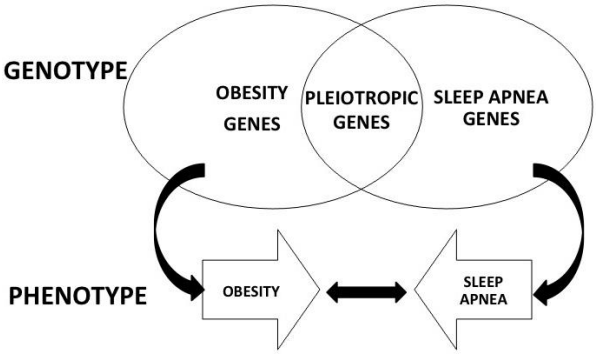

Figure 1. Genetic polymorphism of OSA and obesity (adapted after Patel S[21]).

Both obesity and OSA are the result of clinical expression of the inner genotype[21].

There are susceptibility genes that code a specific OSA or obesity phenotype but because the two pathologies interconnect, this genes determine indirect phenotypic influences towards either one of the pathologies[21,22].

There are pleiotropic genes that code a single product which is used by various cells or has a function used by more than two targets which has the role of obtaining the individual desired effect (example: leptin mediator, regulation of fat deposit)[21,23]. Leptin influences both OSA and obesity through independent mechanisms : fragmented sleep decreases the levels of leptin and predisposes to obesity and the fat tissue increases the levels of leptin which acts upon the satiety center in the hypotalamus [24,25].

Another way of evaluating the link between obesity and OSA is by studying the interaction between the genes and the environment, through the side effects of obesity and OSA, interpreted as stress factors of the environment (figure 2) [21].

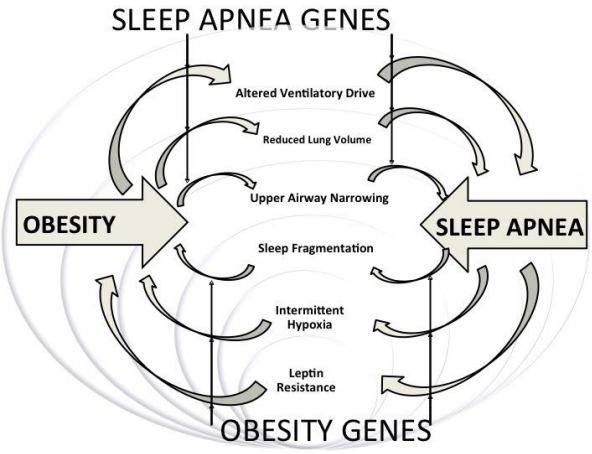

Figure 2. The link between obesity, OSA and environment (adapted after Patel S [21])

Any mechanism that determines obesity or OSA is kept under the incidence of individual genetic susceptibility. The fat deposit in the cervical region determines a characteristic individual response in addition to apnea when preexisting with the lack of cervical muscular ability of reacting to this stress factor [21,26,27].

The genetic polymorphism of obesity determines the degree of pulmonary ventilation implication, the reduced pulmonary volume and the upper airway obstruction[23]. Other polymorphisms decide the degree of impact that obesity has in developing sleep apnea [27].

The impact between OSA and obesity association in children

Obese children have an excessive accumulation of adiposity on the entire body.

The accumulation of fat in the cervical region determines the narrowing of the upper respiratory airways with a potential colaps of these airways, predisposing to apnea[28,29]. Fat tissue around the thorax and the abdomen can cause pulmonary chronic involvement. This appears

due to reduced pulmonary residual volume, reduced number of thoracic trips and increasing need for oxygen[28,30].

There is an interconnection between the pathophysiological mechanisms secondary to sleep fragmentation in obese children and their reaction upon the organism, determining in this way the cardiovascular and metabolic complications (figure 3)[4].

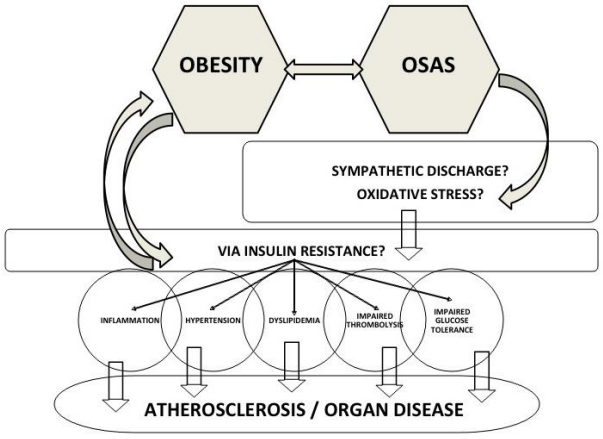

Figure 3. The association between OSA - obesity – metabolic syndrome - cardiovascular complications (adapted after Arens R and Muzumdar H[4])

The most frequent cardiovascular complications that OSA can determine in obese children are: hypertension, ventricular hypertrophy or alteration of regulator mechanisms of blood pressure[6]. Cardiovascular complications seen in obese children with OSA are directly proportional to the degree of upper airway obstruction[31].

The mechanisms that lead to cardiovascular abnormalities and hypertension in children with OSA are being triggered by hypoxia, oxidative stress and increase in sympathetic activity[32,33]. Responsible of these are also some vascular pro-inflammatory factors (C reactive protein, TNFα, IL-6) that can determine endothelial malfunction and thrombotic activation[33,34].

Studying the connection between obesity, metabolic syndrome and OSA, it is shown that OSA can determine hypertension, dyslipidemia, vascular inflammation mediated by increasing resistance to insulin[4]. These effects appear as a result of mechanisms that originate in the oxidative stress, increased sympathetic activity and endothelial malfunction (low nitric oxid level, increased endothelin-1 level, endothelin tissue death, an increased level in serum aldosterone), intermittent hypoxia, fragmented or insufficient sleep[4].

The metabolic syndrome can appear as a complication in the evolution of an obese child[4,35]. The metabolic syndrome was first described in the adult population and the criteria that defines it for the pediatric population still remains a challenge[6,36]. The metabolic syndrome is a clinical entity defined by abdominal obesity, modification of the biochemical lipid profile, increase resistance in insulin, hypoglycemia, hypertension, diabetes, the presence of pro-inflammatory factors and pro-thrombotic factors[28]. It is well known, at this moment, that the risk of developing the metabolic syndrome increases with 50% amongst children with high obesity[6,37]. The results in studies carried out amongst obese children in preadolescent age[38,39] show the association between OSA and increased insulin resistance with an improvement of this parameter proportional with the OSA correction.

In nonobese children or in children with moderate OSA, the association with metabolic syndrome is not seen[38,40] suggesting that OSA in children is a risk factor for developing dynamic metabolic syndrome changes just in presence of obesity. Increased insulin resistance appears secondary to a high concentration of free fatty acids through the reduced inhibition of lipoprotein lipase activity from adipocites[4,41]. This mechanism determines hypertriglyceridemia, hypercholesterolemia, increased LDL-cholesterol and decreased HDL-cholesterol[4,42].

Leptin is a hormone produced by adipocites with an important role in regulating body weight and modeling ventilator response[25,28]. Maintaining the body weight occurs when leptin stimulates the satiety center in the hypothalamus and the efficiency of the ventilation response is directly proportional with the degree of obesity and sleep disordered breathing[28,43].

The lack of sleep or fragmented sleep inhibit the production of leptin, therefore the lack in stimulation of the satiety center by the leptin becomes a potential mechanism of very early obesity development[28,43,44].

In obese children, hyperleptinemia appears to produce a cellular desensitization, triggering resistance to leptin and inhibiting leptin's effects [28,45]. Resistance to leptin is secondary to pro-inflammatory cytokine action[46,47].

Sleep fragmentation determines, beside the reduction in the serum level of leptin, an increase in the serum level of ghrelin, a hormone that stimulates the appetite and that determines obesity and aggravation of OSA[28,44,48].

Through these mechanisms, the sleep disorders and obesity interact and act upon each other, resulting in various effects.

Management of obese children with OSA

Obese children have a high risk of developing OSA and due to this high risk the American Society of Paediatrics recommend a thorough evaluation of every snoring child[2].

The approach of a snoring child means a thorough evaluation of the child's history of complaints, the application of specific health questionnaires as well as a good and detailed clinical and pathological examination[3,4.]

A good night's sleep influences every day quality of children's life and this is why snoring, fragmented sleep, daytime excessive sleeping need screening and a careful medical examination[2] from medical specialists (paediatrician, ENT, neurologist, pneumologist, psychiatrist).

Nowadays, polisomnography is considered as being the "gold-standard" in diagnosing OSA[2]. Investigations like nocturnal pulsoximetry, polisomnography perform only during a daily sleep episode, video-recordings, do not offer at the time being sufficient information to support the diagnosis of OSA in children[2,4]. The management of obese children with OSA includes prevention and therapeutical measures[2]. Some of the most important therapeutical pathways that are recommended in children with OSA are educational strategies for a good sleep hygiene, changes in eating habits, anti-nasal devices, medication, continuous positive airway pressure therapy, surgery (figure 4)[2,4.]

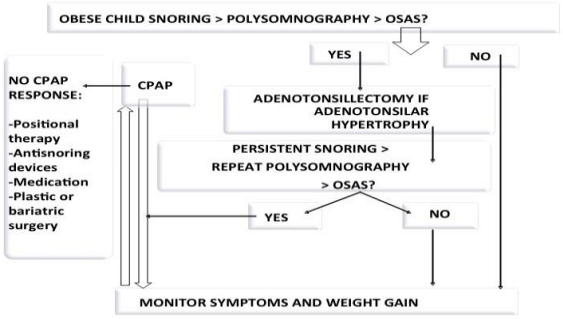

Figure 4: Approaching an obese child with OSA (adapted after Arens R and Muzumdar H [4])

The management of obese children with OSA and adenotonsillar hypertrophy imposes adenotonsillectomy and regular follow-ups (20). The American Academy of Sleep Medicine advices monitoring through polisomnography after performing the adenotonsillectomy of every obese child with OSA (20).
Friedman M *et* al. in the meta-analyse from 2009 observes that 59.8% of obese children diagnosed with OSA that underwent a surgical procedure (adenotonsillectomy) had a good postoperative evolution with a fully solved OSA defined by apnea:hypopnea index <1 event/hour[49].
When OSA is due to other causes or persists after adenotonsillectomy, the apnea:hypopnea index >1 event/hour or when the tonsillectomy can not be performed, the advice is for continuous positive airway pressure treatment (CPAP)[20]. CPAP therapy is one of the options that have been proven as efficient amongst the paediatric population diagnosed with OSA[20].
Other treatment methods for obese children diagnosed with OSA are represented by :

- anti-snoring devices: nasal devices (nasal strips, nasal dilators); oral devices (chin strips, vestibular shield, mandibular repositioning splint[20,50]
- plasty: uvulopalatopharyngoplasty, uvulopalato-plasty; soft palate implants[4,51]
- medication: saline nasal solutions, nasal decongestants, antihistamines, steroids, oral therapy with antileukotrienes[20]
- weight loss - is considered a good treatment for obese children with OSA[4].

Weight loss can be helped by changes in eating habits or through bariatric surgery[4]. Practically, the applicability of this treatment method amongst the paediatric population is difficult due to low long term compliance towards advices and recommendations regarding food habits[4,20].
Bariatric surgery in children can be considered a one therapeutic option in cases where we find morbid obesity, in children that have reached bone maturity and where all of the other ways of weight loss have failed[4,52].
The improvement of OSA symptoms amongst obese children once they have lost weight is shown through an improvement of the respiratory effort that comes as a consequence of fat tissue reduction and through an improvement of the sleep quality[53].
The management of OSA amongst obese children needs careful consideration and thorough knowledge of the two compounds that form this entity and only a multidisciplinary team with vast experience in this therapeutic pathways can reach a success.

CONCLUSIONS

Future research is needed both for a better understanding of the mechanisms by which OSA and obesity interact and for developing the best therapeutical interventions in children.
A good night's sleep influences every day quality of children's life and this is why snoring, fragmented sleep, daytime excessive sleeping need screening and a careful medical examination from medical specialists (pediatrician, ENT, neurologist, pneumologist, psychiatrist). Polisomnography is the gold-standard in evaluation of a snoring child and adenotonsillectomy is the first-line treatment for children with sleep-related disorders breathing. Obesity is a risk factor for OSA and reduces the success rate of adenotonsillectomy.
The management of a snoring child is a complex process that includes educational strategies for a good sleep hygienne, use of anti-snoring devices, medication and surgery.
The variability of risk factors involved in the daily modelling of a child's behaviour and his neurocognitive development, as well as the ones involved in the complications rate, determines the perfecting progress and continuous evaluation of diagnostic and treatment methods.

Acknowledgement *This work was co financed from the European Social Fund through Sectoral Operational Programme - Human Resources Development 2007-2013", project number POSDRU/1871.5/S/155605, entitled "Scientific excellence, knowledge and innovation through doctoral programs in priority areas", Beneficiary – University of Petrosani.*

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