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Reviews

Obstructive sleep apnea: from the beginnings, to the risk factors and to occupational medicine assessment

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Abstract

Over the last thirty years, the pathogenesis of obstructive sleep apnea syndrome (OSAS) has begun to be elucidated worldwide due to the presence of standardized diagnostic and treatment. In adults, the clinical diagnosis may be suggestive of OSAS when symptoms like fatigue, lack of concentration, poor work performance, absenteeism, daytime sleepiness, insomnia, snoring, nocturnal respiratory distress or apnea episodes witnessed by others are present. Some medical conditions found in employees' personal history such as craniofacial abnormalities, some endocrine diseases, arterial hypertension, especially resistant arterial hypertension, coronary artery disease, atrial fibrillation, congestive heart failure, stroke**,** obesity, diabetes mellitus, cognitive dysfunction or mental disorders may be the alarm signal for OSAS. The assessment of all risk factors, clinical presentation and diagnosis must become an important part of occupational medical examinations and performed in all workers due to its major public health potential and impact on survival. The early identification of OSAS among workers performed by the occupational physician can potentially reduce the risk of work injuries and fatalities. In conclusion, OSAS is a complex entity and an important public health problem. The delay in diagnosis and treatment contributes to the increase of healthcare services demand and implicitly to general mortality.

Keywords: *sleep-disordered breathing, snoring, obstructive sleep apnea, obesity, smoking*

Introduction

Sleep-disordered breathing issues associated with poor work performance and traffic accidents are considered a non-occupational pathology with the highest risk of occupational injuries, gaining an increasing share of morbidity and mortality. Several sleep medicine reviews assessed a relationship between sleep problems, snoring, obstructive sleep apnea, excessive daytime sleepiness and work accidents, illness, absenteeism, loss of productivity, decrease in employee well-being, and above all, traffic accidents among professional drivers with unknown and untreated OSAS [1-6]. The roots of sleep-disordered breathing (SDB) are found in the nineteenth century in "The Posthumous Papers of the Pickwick Club", in which Charles Dickens describes Joe as being "an obese boy with loud snoring and excessive sleepiness" [7]. This "fat boy with irresistible hypersomnolence" character would make history in sleep medicine, becoming the prototype of the OSAS patient [7-10]. Pickwickian Syndrome coined by Burwell, Robin et al in 1956 was later on named by other investigators Obesity Hypoventilation Syndrome (OHS) [8, 10].

Table 1 Clinical risk factors for OSAS (adapted after Sharma et.al., 2014) [18]

1. Socio-demographic risk factors	- age - sex - race
2. Risk factors supported by strong scientific evidence	- obesity - central adiposity disposition - neck circumference - craniofacial abnormalities
3. Potential risk factors	- genetic predisposition and family history - smoking - alcohol consumption - pregnancy - menopause - endocrine disorders

Research studies conducted by Gastaut [11], Jung and Kuhlo [12] showed that there is a relationship between SDB and upper airway (UA) collapse, thus recognizing OSAS [9-12]. In 1972, Lugaresi and Sadoul organized the first international symposium on "Hypersomnia with Periodic Breathing" in Rimini, Italy, which will serve as a launch ramp for increasing interest and research in the field of SDB during sleep [13]. Four years later, in 1976, Guilleminault et al. [14] identified and defined sleep apnea syndrome (SAS) as well as OSAS among even nonobese patients, and Sullivan et al. [15] devised in 1981 the first special machine with nasal continuous positive airway pressure (CPAP) used for OSAS therapy [13].

Over the last thirty years, SAS pathogenesis has begun to be elucidated worldwide using standardized diagnostic and treatment for this disease. OSAS is characterized by obstruction and collapse of the UA causing increased respiratory effort and inadequate ventilation. It differentiates from central sleep apnea syndrome (CSAS) by the pathophysiological mechanism that causes respiratory distress: in OSAS, the UA obstruction is frequently caused by abnormal anatomy and/or abnormal muscle control designed to maintain UA airway permeability, while during CSAS the central nervous system control of ventilation is affected, leading to loss of respiratory effort. The repetitive nocturnal apnea events during sleep are induced by the collapse of the UA. Fragmented nocturnal sleep architecture and hypoxemia, as well as premature aging are some of the consequences. Brain dysfunctions, expressed by an abnormal daytime sleepiness, absenteeism and poor work performance, loss of concentration, are considered the reason of many traffic accidents among drivers, especially professional drivers. It is remarkable that, despite all the diagnostic advances in the past two decades, 70-80% of OSAS patients remain undiagnosed due to the tendency of patients to seriously underestimate their symptomatology [16,17]. Based on worldwide scientific evidence, frequently applied by the Western culture, a group of researchers from India, Sharma et al [18] proposed in 2014 the first multidisciplinary OSAS guide that was also applicable to developing countries. There are multiple risk factors for OSAS and may be classified into three groups according to the quality of scientific evidence (Table 1). Knowing the risk factors becomes crucial for the occupational health practitioner in the early diagnosis of OSAS in individuals at risk of workplace accidents. In adults, the clinical diagnosis may be suggestive of OSAS when symptoms like fatigue, lack of concentration, poor work performance, absenteeism, daytime sleepiness, insomnia, snoring, subjective reporting of nocturnal respiratory distress or apnea episodes witnessed by others are present. Some medical conditions found in employees' personal history such as craniofacial abnormalities, some endocrine diseases, arterial hypertension, especially the resistant arterial hypertension, coronary artery disease, atrial fibrillation, congestive heart failure, stroke, obesity, diabetes mellitus, cognitive dysfunction or mental disorders may be the alarm signal for OSAS.

The prevalence of OSAS in adults by gender is in favor of men in a ratio of 2-3: 1 (M: F) [19]. It is possible that the symptomatic pattern of SDB may be different between the two sexes because women who have been suspected of OSAS more frequently reported fatigue and lack of energy [20,21] than loud snoring and night awakenings [22]. There are also differences in

reporting nighttime symptoms from bed partners. Thus, female sleep partners seem to have a lower threshold of perception and symptom reproduction than males [23]. Medical personnel suspect less the presence of OSAS in women than in men; it is well known in the scientific field that there is an increased prevalence of this disorder in males.

Age is a contributing factor for OSAS, people aged over 65 have a two times higher risk (20%) of developing OSAS than those between the ages of 39 and 49 years (10%) [24]. Aging also includes the risk of obesity, fat deposition in the adjacent area of the pharynx, structural modification adjacent to the laryngeal body and soft palate elongation, which influences OSAS [25]. Althought Asian ethnicity is less obese than white ethnicity, the prevalence of OSAS in the East is not less than in the West. It was found that for the same age, gender and body mass index (BMI) characteristics, Asians have a higher OSAS severity ratio than whites [26,27]. A future racial classification based on genomic models could provide a new view of OSAS-prone groups [28].

Hormonal influences correlate with aging, OSAS prevalence being higher in postmenopausal women [23], especially in those without estrogen replacement hormone therapy [29,30]. Unlike women, the administration of exogenous androgen therapy in men increases the OSAS severity. The risk factors for OSAS supported by strong scientific evidence include obesity that leads to the acceleration of progression and severity of OSAS by a 10% increase in obesity rate over time [31]. If the overweight defined as a BMI > 27kg/m2 is associated with a 20% increase in OSAS risk [32], morbid obesity defined as a BMI > 40kg/m2 doubles the risk of OSAS [33], than the benefits of reducing body weight with a reduced-calorie diet or bariatric surgery procedures may reduce the severity of OSAS and achieve better control with CPAP therapy [32,33].

What should attract the practitioner's attention in order to suspect OSAS? First of all, the central (visceral) adiposity, often associated with OSAS, increases the volume of adipose tissue adjacent to the pharyngeal airway, predisposing to UA obstruction and also to lung volume reduction by increasing the volume of troncular fat mass and predisposing to pharyngeal collapse. The overlap of metabolic and humoral factors involved in adiposity distribution is followed by additional increase of pharyngeal collapse. Central adiposity increases with age and is associated with postmenopausal women [34]. Obesity correlates with high prevalence of glucose intolerance [35,36] and the occurrence of diabetes [37] in patients with OSAS.UA resistance during sleep is influenced by increasing age and male gender. Physical examination may also reveal neck circumference (NC) as a risk factor for OSAS when it is greater than 43 cm for men and 38 cm for women [38]. Thus, NC measurement becomes an important part of the clinical examination. Regional distribution of body adipose tissue is a more important determinant of AHI than generalized obesity [39] and NC is considered one of the physical characteristics of the patient suspected of having OSAS.

Craniofacial abnormalities are seen from early childhood and are established risk factors for OSAS, especially in normal weight patients [40], modifying the mechanical properties of the UA by reducing their diameter and permeability. Craniofacial and UA morphology are genetically determined and explain racial differences in the prevalence of OSAS. Static cephalometric analysis using radiography, computed tomography and magnetic resonance imaging can reveal skeletal and soft tissue structural differences between individuals with and without OSAS. Craniofacial changes that predispose to OSAS development [41] are:

- nasal obstruction associated or not with deviation of the nasal septum and nasal turbinate hypertrophy: is considered a predisposing factor for UA collapse by increasing nasal resistance followed by a significant development of negative-pressure breathing that is increased by snoring and not by OSAS itself;
- micrognatia: is a small retropositioned mandible which considerably reduces the retrofaringian region, characteristic of patients with Pierre-Robin syndrome;
- downward movement of the hyoid bone: changes the position of the tongue, promoting the collapse of the UA;
- hypertrophy of the uvula, tonsils and soft palate: the state of agglomeration of the oropharynx is common in OSAS and it is due to neck fat deposition associated with obesity that causes soft tissue vibration and snoring;
- macroglossia: the tongue is a predisposing factor for SDB, both in children and adults. In adults, macroglossia is seen in obese and individuals with acromegaly. In children and adolescents, it is frequently found in Down syndrome patients. The Mallampati score used to evaluate the permeability of the oropharyngeal airway should be calculated [42].

Individual genetic susceptibility and family inheritance predispose to OSAS development. First degree relatives of OSAS patients have a 2-fold higher risk of developing this disease than relatives of patients without OSAS and family susceptibility increases directly according to the number of affected family members [43,44]. Obesity appears to be

closely related to OSAS and a familial aggregation of OSAS and obesity may be possible; in addition, apolipoprotein E genotype 4 is particularly associated with OSAS [45].

In this current society, in a full epidemic of sedentary and obesity, smoking is a risk factor for some respiratory and cardiovascular diseases, that induces longer sleep onset latency, inefficient and fragmented sleep, compensatory daytime sleepiness and more and more studies support the interaction between OSAS and smoking [46].

Alcohol consumption is consistent with relaxation of UA dilator muscle activity, increasing their resistance and inducing OSAS in susceptible subjects [47]. Alcohol may prolong the duration of apnea episodes, decreases the frequency of arousals, increases the frequency of respiratory occlusive episodes and the severity of hypoxemia [48].

Pregnancy may protect women against OSAS due to increased progesterone secretion and decreased sleep time in supine position, but on the other hand, may induce respiratory disorders due to gestational weight gain, physiological changes in respiratory function and reduction in pharyngeal muscle tone [49,50]; pregnant OSAS patients are associated with resistant hypertension, higher risk of eclampsia, lower weight and Apgar score at birth [51]. Due to the maternal and fetal implications, those with a high risk of OSAS should be early identified and implicitly treated.

Polycystic ovary syndrome that is characterized by oligomenorrhea, chronic anovulation, central obesity, dyslipidemia, androgenic hormonal excess, insulin resistance and abnormal gonadotrophin secretion has a prevalence of 5-12% [52,53] and is associated with OSAS in 60-70% of the cases in some studies [54-56]. Hypothyroidism might cause OSAS due to low thyroid hormone production and secondary to obesity [57]. Also, hypothyroidism leads to the accumulation of subcutaneous hyaluronic acid, thus contributing to myxedema, mucopolysaccharide impregnation of UA, tongue and pharynx, aggravating the collapse of these structures during sleep, leading to changes in respiratory mechanics, increasing the risk of OSAS.

The International Classification of Sleep Disorders ICSD-3 updated in 2014, divides SDB in 4 categories: OSAS in adult and paediatric individuals, CSAS, sleep-related hypoventilation disorders and sleep-related hypoxaemia. The ICSD-3 classification strengthens the definition of the "respiratory event" found in the previous ICSD-2 classification and emphasizes that obstructive respiratory distress includes not only obstructive sleep apnea and hypopnea, but also respiratory effort-related arousal (RERA). Thus, the individual term UA resistance syndrome [59], characterized by the presence of RERA index ≥ 10/hour of sleep, AHI <5/hour of sleep and minimum nocturnal SaO2 ≤ 92% is discouraged because it is a variant of OSAS and not a separate diagnosis with distinct nomenclature [60]. The latest version of the American Academy of Sleep Medicine (AASM) manual [61] published in 2014, notes and defines respiratory events during sleep and the standardization criteria for these events makes polysomnography the gold-standard method for diagnosing OSAS in adults when 5 or more obstructive respiratory events (obstructive and mixed apnea, hypopnea or RERA) are present per hour of sleep.

OSAS screening is required for all professional drivers. It may be advisable, in addition to inventorize OSAS risk factors and comorbidities, to periodically conduct a survey using Occupational Circumstances Assessment Interview and Rating Scale and Occupational Self-Assessment in order to assess occupational performance.

Conclusion

In conclusion, OSA is a complex disease entity and represents an important public health problem. The delay in diagnosis and treatment contributes to the increase of healthcare services demand and implicitly to general mortality. The assessment of all risk factors for OSAS, clinical presentation and diagnosis must be routinely performed in all workers by their occupational physician. Obtaining data on snoring, nocturnal obstructive breathing symptoms, excessive daytime sleepiness, lack of concentration, absenteeism among workers must become an important part of occupational medical examinations because of its major public health potential and impact on survival. The early identification of OSAS among workers by occupational physician can potentially reduce the risk of work injuries and fatalities.

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