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Sleep disordered breathing: OSA, CSA, Pathophysiology and Diagnosis

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ABSTRACT

Obstructive sleep apnea syndrome (OSAS) is a prevalent disorder that has been reported to occur in 2 to 4% of middle-aged adults. A similar prevalence of OSAS has been reported from India as well. However, this condition is frequently unrecognized and underdiagnosed. Important pathophysiological changes in patients with obstructive sleep apnea (OSA) is an alteration in human upper airway leading to a reduction in cross-sectional area of the upper airway contributing to the easy collapsibility of upper airway during sleep. Other pathophysiological changes in OSA are oxidative stress, systemic inflammation, sympathetic nerve activation, endothelial dysfunction, procoagulant activity, intrathoracic pressure changes and metabolic dysregulation. The gold standard for diagnosis of OSA is full polysomnography.

Key words: Obstructive sleep apnea, Central sleep apnea, Oxidative stress, Metabolic dysregulation, Polysomnography

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INTRODUCTION

Obstructive sleep apnea is a prevalent condition, but frequently unrecognized and undiagnosed. The important phases of sleep are Non-Rapid Eye Movement (NREM) and Rapid Eye Movement (REM) sleep. There is decrease in sympathetic nervous system activity, heart rate, blood pressure, cardiac output, systemic vascular resistance and metabolic rate in NERM stage, but there is an increase in para sympathetic activity during NREM stage. However, there will be intermittent surges in sympathetic activity during Rapid Eye Movement (REM) sleep.

Obstructive sleep apnea :

The OSA is the repetitive interruption of ventilation during sleep caused by collapse of the pharyngeal airway. OSA is defined as reduction in airflow associated with upper-airway collapse or narrowing that occurs during the change from wakefulness to sleep. Apnea due to upper airway collapse is defined as nearly complete cessation of airflow associated with oxygen desaturation or an arousal from sleep and hypopnea is due to partial collapse of upper airways. Apnea is defined as cessation or near complete cessation that is more than 90% reduction of airflow $\geq$ 10 seconds despite continuing ventilatory effort with five or more such episodes per hour of sleep and is usually associated with a decrease of $\geq$ 4% in oxyhemoglobin saturation. Hypopnea is characterized by a reduction of > 50% in airflow for $\geq$ 10 seconds associated with a $\geq$ 3% decrease in oxygen saturation and/or arousal (1).

Central Sleep Apnea (CSA) :

The central sleep apnea (CSA) is the repetitive cessation of ventilation during sleep resulting from loss of ventilatory drive. The manifestations of CSA include high altitude induced periodic breathing, idiopathic CSA, narcotic-induced central apnea, obesity hypoventilation syndrome, and Cheyne-Stokes breathing (2).

Upper Airway Resistance Syndrome :

There will not be significant decrease in airflow in upper airway resistance syndrome, but snoring is usual, 15 or more episodes of arousal per hour of sleep with no significant decrease in oxyhemoglobin saturation are observed in Upper Airway Resistance Syndrome.

Pickwickian Syndrome - Obesity Hypoventilation Syndrome :

This entity consists of obesity, sleep disordered breathing, hypoxia and chronic hypercapnea during wakefulness in the absence of other known causes of hypercapnea. This was described as “Pickwickian Syndrome” in 1956 in a case report as the patient reported in this report resembled a character depicted by Dickens in his book “The posthumous papers of the Pickwick club” because both were obese with excessive hyper somnolence (3).

Apnea-Hypopnea Index :

Apnea-Hypopnea Index (AHI) is the number of apneas and hypopneas per hour of sleep confirmed by electro-encephalogram (EEG). Apnea-hypopnea index (AHI) is used to characterize OSA. Another index that is used is Respiratory Disturbance Index (RDI) and this is the number of apneas, hypopneas and respiratory effort related arousals per hour of sleep confirmed by EEG. The severity of OSA is classified based on apnea hypopnea index. AHI more than 5 and less than 15 events/hour of sleep is mild OSA, AHI between 15 to 30 events/ hour of sleep is moderate OSA and AHI more than 30 events/ hour of sleep is severe OSA. OSAS is defined as sleep disordered breathing associated with daytime symptoms most often excessive daytime sleepiness. It has been estimated that the OSAS affects 2 to 4% of middle-aged adults (4).

Risk factors :

Risk factors for development of OSA are classified as non-modifiable and modifiable factors (2, 3). The non-modifiable risk factors are age, gender (male), ethnicity (being black, Hispanic), anatomical abnormalities of craniofacial regions and upper airway, thick neck with circumference more than 17 inches in males and more than 16 inches in females and a genetic predisposition (5). The modifiable risk factors are excessive body weight (obesity), use of alcohol, sedatives or tranquilizers, narrowed airways due to enlarged tonsils or adenoids, smoking, chronic nasal congestion, hypertension, diabetes mellitus, myxedema and menopause (6). Wisconsin sleep study had identified baseline obesity, older age and presence of snoring as factors important in progression of disease (4).

Upper airway anatomy :

The human upper airway is composed of numerous muscles and soft tissue but it lacks bony support. It has been observed that the cross sectional area of the upper airway during wakefulness is reduced in patients with OSA compared with subjects without OSA, thereby leading to collapse of the upper airway during sleep (7).

Pathophysiology :

OSA-induced biological changes include intermittent hypoxia, intermittent hypercapnia, intra thoracic pressure changes, sympathetic activation and sleep fragmentation (8). Chronic intermittent hypoxia is the cardinal feature of OSA. During intermittent hypoxia, there will be repeated episodes of hypoxia and normoxia resembling ischemia/perfusion events (9). During hypoxic/ischemic phase, the cells adapt to low O2 environment and during reoxygenation/ reperfusion phase, there will be sudden increase of oxygen in the cells resulting in the production of reactive oxygen species (ROS) (9, 10).

OSA can cause sympathetic activation, metabolic dysregulation, endothelial dysfunction, systemic inflammation, oxidative stress, and hyper

coagulation and neurohumoral changes. These changes may lead to hypertension (both systemic and pulmonary), heart failure, arrhythmias, myocardial infarction, stroke and sudden cardiac death. Repetitive episodes of upper airway narrowing and / or occlusion cause hypoxemia, reoxygenation, swings in intra thoracic pressure and central nervous system arousals. These factors can cause acute stress on cardiovascular system and the cumulative effects from these can lead to disruption of cardiovascular homeostatic mechanisms. These may lead to daytime abnormalities in sympathetic nervous system function and to heart rate variability (11).

a) Oxidative stress :

Many studies have reported a role of oxidative stress in patients with OSA (12). Studies had demonstrated that there was an increase in thiobarbituric acid-reactive substances (TBARS) levels in patients with severe OSA compared with healthy control subjects and treatment with continuous positive airway pressure (CPAP) reduced the lipid peroxidation events (13-15). It was also reported that there was an increased level of oxidized low-density lipoprotein levels in OSA. Inhibition of xanthine oxidase by allopurinol and supplemental intake of vitamin C have been shown to improve endothelial function in patients with OSA. Glycation products, the end result of oxidative stress were also reported to be increased in OSA patients with normal glucose homeostasis. The demonstration that urinary 8 - hydroxy - 29 - deoxyguanosine excretion was significantly higher in patients with severe OSA versus control subjects suggests oxidative DNA damage in OSA. The antioxidant capacity in the blood which acts as defense against free radicals has also been found to be reduced in OSA compared to control subjects. In observational studies, a derangement in the oxidant-anti-oxidant balance with a shift towards oxidative stress was documented and treatment with the anti-oxidants (vitamin E, vitamin C and N-acetyl cysteine) had demonstrated a reduction in oxidative stress in OSA patients (15, 16). The results from these studies indicate the occurrence of oxidative stress in patients with OSA. However, there are studies that have not demonstrated increased oxidative stress in OSA (17).

b) Systemic inflammation :

It has been noticed that CD4 and CD8 T cells of patients with OSA undergo phenotypic and functional changes with a shift towards type 2 cytokines dominance and increased IL4 production (18). A marked increase in TNF-α and CD40 ligand in CD8 T cells from patients with OSA was also reported. CPAP treatment improved or reversed all these abnormalities in OSA patients (18, 19). Increased circulating levels of CRP have been consistently reported in both adults (20, 21), as well as in children with OSA (22) and are reduced on effective treatment (20, 23). It has been reported that there is an independent association between severity of OSA and elevated

CRP level in men without comorbidities (24). Nuclear factor kappa B (NF-kB), an important factor for activation of inflammatory pathways, has been found to be increased in OSA (25). Expression of adhesion molecules on circulating monocytes may indicate activation of systemic inflammation in OSA (26). It has been reported that TNF-α -308 polymorphism is associated with OSA (27).

c) Sympathetic Nerve Activation :

An increased sympathetic nerve activity has been reported in OSA (28). The increase in sympathetic activity during sleep may be due to the activation of peripheral chemoreceptors by hypoxia, hyper-capnea and apneas leading to peripheral vasoconstriction and increase in blood pressure (29). It has also been demonstrated that there is exaggerated sympathetic activity during daytime wakefulness despite normoxia (30). Increased concentrations of catecholamines in urine and elevated levels of norepinephrine in plasma were also seen in patients with OSA (31). Muscle sympathetic nerve activity (MSNA) has been found to be elevated in OSA during wakefulness (28) and CPAP therapy reduces the high sympathetic activity. An increase in resting heart rate during wakefulness has been observed in OSA patients suggesting that there is an increase in cardiac sympathetic drive in OSA (32). Thus chronic sympathetic activation may be an important factor for the development of cardiovascular disease in OSA (33).

d) Endothelial dysfunction :

Endothelial dysfunction in OSA is a risk factor for cardiac abnormalities in OSA (34). Endothelial dysfunction in OSA may be due to chronic intermittent hypoxia and to sleep loss and fragmentation. The endothelial dysfunction results in increased vasoconstriction and reduced vasodilation. Nitric oxide which is a powerful vasodilator is decreased in OSA and the decreased levels of nitric oxide may contribute to reduced vasodilation and platelet adhesion and aggregation. Treatment of OSA has been found to increase nitric oxide levels in OSA (35). Recurrent hypoxemia has been found to increase the endothelin levels in OSA and there is a reduction in endothelin levels on treatment with CPAP (36). Endothelin is a potent vasoconstrictor which causes elevated blood pressure. Endothelial dysfunction is one of the important factors that are responsible for cardiovascular diseases in OSA.

e) Procoagulant activity :

Several studies in OSA patients had shown that there are elevated levels of plasma fibrinogen, exaggerated platelet activity and reduced fibrinolytic activity suggesting that there is a hypercoagulable state in OSA (37). The exaggerated platelet activity has been found to be reduced following treatment with CPAP (38). There is also an increase in mean platelet volume which has been reduced by CPAP therapy in OSA patients.

f) Intrathoracic pressure changes :

During obstructive sleep apnea, the repetitive inspiratory efforts against a closed upper airway lead to increased negative intrathoracic pressure. As a result, there will be an increase in transmural gradients across the atria, ventricles and aorta. This is similar to the Muóller maneuver in which an individual inspires against closed glottis leading to a pleural pressure of -30 cm H_2O (39). These changes in transmural gradients can result in autonomic and hemodynamic instability (30, 40). An increase in aortic transmural pressure can cause aortic dissection in OSA patients.

g) Metabolic dysregulation :

There are evidences suggesting that OSA is independently associated with metabolic syndrome (41). Chronic intermittent hypoxia and sleep deprivation with sleep loss may play a role to trigger inflammation leading to metabolic syndrome. OSA may be a risk factor for metabolic syndrome. Obesity particularly central adiposity is a potent risk factor for sleep apnoea (42). An interaction of obesity-OSA-metabolic syndrome involving many mechanisms has been postulated (43). The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) report recommends the use of five variables (hypertension, insulin resistance or glucose intolerance, low serum high-density lipoprotein (HDL) cholesterol, elevated serum triglyceride, and abdominal obesity) with set threshold values for each variable for clinical characterization of metabolic syndrome. Subjects meeting three of these five criteria are classified as having metabolic syndrome. The cut off value for defining abdominal obesity may vary based on ethnicity (44). Features associated with metabolic syndrome are pro inflammatory state, prothrombotic state, hyperleptinemia, hypo-adiponectinemia, hyperuricemia, endothelial dysfunction and microalbuminuria (45).

Diagnosis :

Diagnosis of OSA is based on symptom assessment, clinical examination and laboratory investigations mainly by polysomnography.

a) Symptom assessment :

Symptoms can occur during sleep and during wakefulness. The most common symptoms during sleep are snoring, snorting, choking attacks terminating a snore and witnessed apneas by bed partner. Other nocturnal symptoms include non - restorative sleep, nocturnal restlessness, vivid dreams, gastroesophageal reflux, insomnia with frequent awakenings, nocturia, hyper salivation and diaphoresis. Symptoms reported during awake are excessive daytime sleepiness, lack of concentration, cognitive deficits, mood changes, morning headaches, dry mouth, impotence and decreased libido. The severity of excessive daytime sleepiness can be subjectively assessed by questionnaires; the most commonly used

questionnaire is Epworth Sleepiness Scale. Objective tests that can assess excessive daytime sleepiness include Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT) and the Osler Test, but these tests are costly and time consuming (46). The interview of the partner is also important while assessing the patients with suspected OSA.

b) Clinical features :

The clinical features associated with OSA are obesity (particularly central, body mass index more than 30 kg/m^2), large neck circumference (more than 40 cm), narrow mandible, narrow maxilla, retrognathia, dental malocclusion, overbite, reduced nasal patency, high and narrow hard palate, elongated and low-lying uvula, enlarged tonsils, enlarged adenoids and macroglossia. Clinical examination of a patient suspected to be suffering from OSA includes measurement of blood pressure, cardiorespiratory auscultation, examination of the oral cavity and noting the presence of teeth and dentures. The assessment of the tonsils, tongue size, architecture of hard palate and faucal pillars are important. Mallampati score can be used to assess the upper airway in OSA.

c) Laboratory diagnosis :

The "Gold standard" for the diagnosis of OSA is full polysomnography and it provides detailed information on sleep state and respiratory and gas exchange abnormalities (47). Other variables assessed during polysomnography are body position, heart rate and rhythm, and muscle tone and contraction. Polysomnography is resource intensive requiring a full sleep laboratory and a trained technician. A minimum of 12 channels of recordings that include electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), oronasal airflow, chest wall effort, body position, snore microphone, electrocardiogram (ECG), and oxyhemoglobin saturation are usually used in polysomnographic (PSG) studies. The duration of the diagnostic study should be at least 6 hours.

However, when there is an obvious case of OSA, split-night studies, in which the first half of the study night is used for diagnosis and the second half to monitor treatment response using CPAP are also used. Because of the cost factor and the requirement of a trained technician, home-based sleep studies involving limited cardiorespiratory assessments are also advocated as an alternative to hospital based detailed polysomnographic studies. Cardio-respiratory monitoring which involves the measurement of airflow, respiratory effort, oxygen saturation and heart rate, but not EEG has been used to assess sleep apnea. Overnight oximetry is also used as a screening test to evaluate suspected cases of OSA by continuous recording of oxygen saturation (SaO2) during sleep. The characteristic pattern of desaturation in OSA is repetitive desaturation and oximetry may therefore be useful in

evaluation of severe cases of OSA, but not in mild or moderate cases. There are many other conditions such as COPD, kyphoscoliosis, muscular dystrophy etc. that cause hypoxemia. Therefore, the observation of hypoxemia alone by oximetry cannot be taken as a diagnostic criterion of OSA.

A task force of the American Academy of Sleep Medicine has recommended the following criteria for the diagnosis of OSAS (48) and the patient suspected of OSAS must fulfil criterion A or B, plus criterion C:

A. Excessive daytime sleepiness that is not better explained by other factors

B. Two or more of the following that are not better explained by other factors:
Choking or gasping during sleep
Recurrent awakenings from sleep
Unrefreshing sleep
Daytime fatigue
Impaired concentration

C. Overnight monitoring demonstrates five or more obstructed breathing events per hour during sleep. These events may include any combination of obstructive apneas/hypopneas or respiratory effort–related arousals (49).

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