Sleep Apnea

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ABSTRACT
Sleep apnea is a potentially life-threatening condition with numerous negative metabolic, psychologic and cognitive effects. Although suspicion of sleep apnea can be obtained from the history and physical exam, the gold standard for diagnosis is polysomnography (PSG). In most cases, the cause of sleep apnea is secondary to upper airway obstruction. The treatment of sleep apnea varies depending on its severity, which can be quantified using PSG. Treatment options include lifestyle modification, oral appliances, positive airway pressure and upper airway surgeries. This paper reviews the current literature on epidemiology, genetics, diagnosis and management of sleep apnea.

INTRODUCTION
Sleep is essential for normal physiologic and metabolic homeostasis, with individuals spending an average of one third of their lifespan sleeping. Naturally, its disruption can be detrimental to a person’s health and well-being. Over the last century, sleep research has provided interesting insight into the normal functions of sleep and associated disorders. The following article will review the current understanding of sleep apnea, the most studied disorder in sleep medicine.

NORMAL SLEEP CYCLE
Sleep consists of two general stages: non rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM is divided into three stages: N1, N2 and N3, based on electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (EMG) characteristics.1

The majority of sleep is spent in NREM sleep, which is associated with decreased brain and EEG activity. In contrast, REM sleep is characterized by a fast-frequency and low-voltage EEG tracing similar to an awake pattern. The hallmark feature of REM sleep is the presence of rapid eye movements with paralysis of all other voluntary muscles, defined by an atonic EMG.

A typical night of sleep consists of four to five cycles of REM and NREM sleep, which last 90-100 minutes each. An awake individual will drift into N1 briefly before proceeding into N2 and subsequently N3 and REM sleep. Deep sleep (N3) predominates in the first half of the night, while individuals alternate between N2 and REM sleep in the second half.2 Many physiological changes occur during both NREM and REM sleep involving the autonomic nervous system, respiratory, cardiovascular, gastrointestinal, endocrine and genitourinary systems.3

PATHOGENESIS
To accommodate for the complex functions of speech, swallowing and breathing, the oropharynx and hypopharynx are dependent on dilator muscles, notably the genioglossus and tensor palatine, and soft tissues to maintain patency. Obstructive sleep apnea (OSA) is a consequence of pharyngeal collapse that occurs during sleep, resulting in recurrent upper airway obstruction. Anatomical factors play an important role in OSA pathogenesis; the combination of enlarged soft tissue with anomalies in the craniofacial structures may result in narrowing of the upper airway lumen, consequently predisposing individuals to pharyngeal collapse.4 While awake, airway patency is maintained by increased pharyngeal dilator muscle activity, which counteracts the collapsing force of the negative pressure generated during inspiration.5 Sleep results in the loss of this neuromuscular compensation, leading to...
collapse of the airway. The loss of pharyngeal muscle activity and tone is greatest during REM sleep.

The reduction or cessation of airflow causes hypopnea or apnea events, which lead to hypoxia and hypercapnia and stimulate increasing respiratory effort until sleep arousal occurs. Arousal allows for restoration of pharyngeal dilator muscle activity, establishing airway patency. After hyperventilation to correct the blood gas abnormalities, the patient returns to sleep, allowing the cycle to restart and causing recurrent sleep arousal and fragmentation. Ventilatory control instability, measured by loop gain, may contribute to the development of OSA by causing fluctuating upper airway mechanics. Additional contributory factors include differences in sleep arousal thresholds and lung volume.

**Epidemiology and Risk Factors**

Apnea is defined as a cessation of airflow for more than ten seconds. Obstructive apnea involves a loss of airflow with maintained respiratory effort. It is secondary to collapse of the upper airway and is commonly accompanied by oxygen desaturation. Central apnea occurs with the loss of both airflow and respiratory effort, and is usually caused by neurologic disorders, stroke and other metabolic disorders. Mixed apnea episodes are characterized by signs of both obstructive and central apnea. Finally, hypopnea events are defined as a decrease in airflow of at least 30% for ten seconds, with a 4% reduction in oxygen saturation.

Using the above criteria, the apnea-hypopnea index (AHI) and the respiratory disturbance index (RDI) are calculated. AHI is determined by the number of apnea and hypopnea episodes per hour, while RDI is the relationship between the number of apnea, hypopnea and respiratory effort-related arousals per hour. According to the American Academy of Sleep Medicine (AASM), severity of sleep apnea is based on the RDI, with less than 15 classified as mild, 15-30 as moderate and greater than 30 as severe.

A variety of studies have investigated the prevalence of OSA in countries around the world such as the United States, Australia, Spain, Hong Kong, Korea and India. The prevalence of OSA ranges from 3% to 7% for adult men and 2% to 5% for adult women in the general population, with OSA defined as an AHI greater than five events per hour accompanied with excessive daytime sleepiness. It is of interest that the prevalence of OSA is about 24% for men and 9% for women if the only requirement for diagnosis is an AHI greater than five. Hormonal differences may play a role in the effect of gender on OSA prevalence since post-menopausal women have higher rates of OSA compared to pre-menopausal women. Also, post-menopausal women on hormonal therapy have a similar prevalence of OSA compared to pre-menopausal women, indicating a protective role for estrogen. Anatomical factors may also account for some prevalence differences between males and females.

Many studies have shown that, while the prevalence of OSA increases with age, the trend plateaus after 65 years. Possible mechanisms include the effect of age on pharyngeal anatomy that predisposes to collapse of the pharynx. It has been suggested that sleep apnea in the elderly is clinically different from OSA with more characteristics of central sleep apnea.

Obesity and its associated measures such as body mass index (BMI), neck circumference and waist-to-hip ratio are known to be major risk factors for OSA. Weight gain increases the risk of developing OSA while weight loss decreases the AHI and severity of OSA. Smoking has been shown to increase the risk of OSA by three-fold, though the effect is suspected to be reversible through smoking cessation. Alcohol consumption has also been shown to increase apnea and hypopnea acutely but its chronic effects remain controversial. Additional risk factors include craniofacial and upper airway soft tissue and skeletal abnormalities. Nasal obstruction also contributes to OSA by predisposing to airway collapse due to open-mouth breathing. Finally, OSA may have a genetic basis, as its pathophysiology is affected by heritable factors such as craniofacial morphology, fat distribution and variations in neural control of airway muscle tone and breathing.

**Clinical Evaluation**

**History**

Excessive daytime sleepiness, described as fatigue, tiredness or a lack of energy, is a common presenting complaint of OSA. OSA results in daytime somnolence because apneic and hypopneic events cause recurrent arousal, diminishing the restorative effects of sleep. Unfortunately, daytime sleepiness due to nocturnal arousal may be underestimated by both the patient and physician because of its insidious onset and chronic nature. Patients are often unaware of any problems until they begin to affect their daytime performance and quality of life. It is also interesting to note that women are more likely to present initially with insomnia.

Complaints about loud snoring may also prompt patients to seek medical attention. As a result, input from partners and family members is valuable because they may report witnessed apnea events and provide additional information about daytime sleepiness. Other manifestations of OSA include morning headaches, irritability, personality or mood changes, depression and sexual dysfunction.
Physical Examination

The goal of the physical examination is to identify anatomic abnormalities that may predispose to OSA and to attempt to characterize the level of pharyngeal collapse and obstruction. However, the best method to assess the obstruction level remains controversial.26

General findings that are associated with or predispose to OSA include obesity, hypertension and other endocrine disorders. The physical examination consists of the use of flexible nasopharyngoscopy to evaluate the craniofacial morphology, nasal passages, oral cavity and pharynx. Throughout the examination, it is important to note craniofacial abnormalities in the maxilla and mandible as well as other skeletal, dental and soft tissue anomalies.27 The nasal examination should include assessment by anterior rhinoscopy for signs of obstruction such as nasal valve collapse, septal deviation, turbinate hypertrophy, mucosal swelling, rhinorrhea, or presence of polyps or masses.27 Adenoid hypertrophy or the presence of other masses in the nasopharynx should be noted. The oropharynx is evaluated for tongue, tonsillar or uvular enlargement, which can be quantified with the Mallampati score.27 Lateral pharyngeal hypertrophy or banding of the posterior pharyngeal wall is also evaluated.27 The hypopharynx and larynx are also assessed for any masses, lesions or other pathologies such as that may predispose to airway collapse.28

The Muller maneuver is a useful technique to evaluate the level of obstruction in OSA.28 It is performed by introducing the scope into the pharynx, asking the patient to inhale forcefully against closed mouth and nostrils to create negative pressure, thereby endoscopically visualizing where the collapse occurs in the airway. Drug-induced sleep videodoscopy may be even more effective in identifying the level of obstruction because sleep is induced, resulting in a more accurate reflection of the upper airway in OSA.28

DIAGNOSIS

A complete history and physical examination help identify patients suspicious of sleep apnea. A patient’s severity of snoring, neck circumference, BMI, observed apnea and hypertension are correlated with more severe OSA.29 A diagnosis of sleep apnea is confirmed by a formal overnight polysomnography (PSG). PSG determines the presence, severity and the form of the dyssomnia (obstructive, central or mixed).30 Variables measured during a PSG include type and duration of sleep stage (via electroencephalography), eye movements (via electrooculography), limb movement (via electromyography), body position, heart rate (via electrocardiography), oxygen saturation, nasal or oral airflow, respiratory effort and severity of snoring. A more specific test to identify excessive daytime sleepiness is the multiple sleep latency testing (MSLT) where sleep latency following multiple naps during the day is assessed.

Other causes of excessive daytime sleepiness need to be considered, and include narcolepsy, periodic limb movements of sleep as part of restless legs syndrome, or rotating shift work. Respiratory diseases or severe gastroesophageal reflux disease may also mimic OSA. These differential causes of daytime sleepiness make PSG essential to the diagnosis of OSA.

CONSEQUENCES OF SLEEP APNEA

Untreated sleep apnea has multiple negative medical, social and economical consequences. Prolonged hypoxemia has detrimental neurological and cognitive effects including memory loss, decreased verbal and visual learning, and impairment in attention and concentration.31 Sleep apnea also increases an individual’s risk for motor vehicle accidents. A study of Canadian drivers found sleep apnea patients had a 3.0-4.8 fold increase in rate of accidents compared to control subjects.32 In 1999, untreated sleep apnea patients used physician services two times more than controls and incurred $3.4 billion in additional medical services in the U.S.33

Obstructive sleep apnea is associated with hypertension, coronary artery disease, arrhythmias, stroke and diabetes. The prolonged hypoxemia and CO₂ retention in OSA lead to autonomic dysfunction and inflammatory overstimulation, which cause increased cardiac sympathetic drive.34 OSA patients have higher levels of serum cytokines, C-reactive protein, serum amyloid-A, adhesion molecules, which lead to atherosclerosis and endothelial lining dysfunction.35 Increased workload on the cardiac system in OSA leads to higher rates of myocardial infarction (MI), heart failure and pulmonary hypertension.36 Interestingly, OSA patients are more likely to develop an acute MI between 10 p.m. and 6 a.m. as compared to control subjects, whose risk is higher during daytime.37

TREATMENT OF SLEEP APNEA

The management of sleep apnea varies with severity of the apnea, the patient’s complaints and their quality of life. Primarily, it is important to identify factors associated with sleep apnea that need to be addressed, as well as to determine which patients would benefit from medical or surgical management. In most sleep centres, an AHI over 30 is used as an indication for treatment. Overall, the goal of treatment is to improve the sleep cycle, reduce apneic episodes and improve quality of life.

Initial management includes lifestyle modification such as weight loss, exercise and improved nutrition. One prospective study showed that 10% reduction in weight loss improved severity of sleep apnea in 26% of individuals.38 Specialized pillows and belts are used to prevent sleep in a prone position, which can help prevent upper airway obstruction in those with snoring and mild sleep apnea.39 Oral dental appliances used during sleep can advance the mandible and improve AHI and snoring, however they are expensive and require continuous readjustments.40 The most commonly used, non-invasive and effective management of sleep apnea is continuous positive airway pressure therapy (CPAP). A nasal or oral mask is attached to a machine that
provides continuous or intermittent positive pressure therapy, preventing airway collapse. CPAP has been proven in multiple studies to improve subjective sleepiness and cognitive function, and decrease AHI, the risk of MI and the risk of stroke. However, CPAP treatment is a lifelong commitment and the average adherence rate is low, ranging from 60% to 70%. In severe cases or non-compliant CPAP patients, surgical interventions may be a reasonable option. Surgical intervention is successful if it targets the actual site of upper airway obstruction. Nasal obstruction causing snoring or negative inspiratory pressure can be relieved by simple septoplasty and turbinate reduction surgery. The most common site of oropharyngeal obstruction is at the soft palate and is relieved by uvulopalatopharyngoplasty (UPPP), which involves resection of the uvula, tonsils and part of the soft palate to remove redundant tissue and open up the airway. UPPP can also be done in the office under local anesthetic using a laser or radioablution. UPPP is dependent on proper patient selection, based on site of pharyngeal collapse, and success rates as high as 80% have been reported. However, the long-term success of UPPP in the treatment of OSA has been questioned, as one study determined that only 30% of patients showed sustained improvement after three years.

Hypopharyngeal obstruction from tongue can be alleviated with radioablation of the posterior tongue or repositioning the insertion of genioglossus muscle by advancement genioplasty. Another surgical option is maxillomandibular advancement (MMA). While MMA success rate have been reported as high as 90%, it remains a last resort due to its invasive nature.

CONCLUSION

Sleep apnea is a very prevalent and underdiagnosed disease. It has the potential of significant negative consequences in different aspects of an individual’s life including health, wellness, work and safety. Individuals presenting with symptoms consistent with sleep apnea should be offered PSG. Multiple interventions including lifestyle modification, medical and surgical interventions exist, most requiring lifelong commitment.

REFERENCES

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