

Chapter 130

Consequences of Obstructive Sleep Apnea-Hypopnea Syndrome

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INTRODUCTION

Obstructive Sleep Apnea-hypopnea syndrome (OSAHS) is a largely under-recognized and under-diagnosed clinical entity¹. The disease affects upto 2-4% middle-aged men and women in the western population². The clinical presentation may be nonspecific and the reduced awareness of this disorder among clinicians contributes to delayed diagnosis.

OSAHS is characterized by repetitive episodes of asphyxia, hypoxemia and sleep fragmentation. These episodes lead to chemo-reflex mediated sympathetic nervous system activation (arousal) and endothelial dysfunction by oxidative stress which has profound effects on the cardiovascular, neuro-endocrine and other systems³. In this review we shall focus on these systemic consequences of OSAHS.

CLINICAL PRESENTATION

The classical clinical presentation includes snoring and episodes of witnessed apneas or nocturnal choking. There is lack of refreshing sleep and most patients have excessive daytime sleepiness (EDS). The episodes of nocturnal breathlessness have to be differentiated from other causes such as left heart failure, asthma, stridor and cheyne-stokes respiration. The other nonspecific symptoms which bring these patients to various specialty clinics are protean, and include morning headache, epilepsy, behavioral problems, depression, nocturia, impotence and erectile dysfunction¹.

DIAGNOSIS OF OSAHS

OSAHS is characterized by recurrent episodes of obstructive apnea or hypopnea associated with EDS and nocturnal symptoms. The diagnosis of OSAHS is

confirmed by polysomnography. The type of apneas can be classified into central, obstructive, or mixed apneas based on the polysomnographic findings.

The presence and degree of OSAHS is described by apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) which is the measurement of breathing events recorded during sleep over a period of time, expressed as events per hour⁴. Apnea episodes are periods of cessation or marked decrease of airflow for ≥ 10 seconds associated with arterial oxygen desaturation.

Hypopnea has been defined differently by various authors due to lack of a standard definition and has contributed to variance in AHI⁵. The most widely used definition is a reduction in airflow by $\geq 50\%$ associated with arterial oxygen desaturation $\geq 4\%$ or electroencephalographic evidence of arousal. Even though the oxyhemoglobin desaturation may be less severe than apnea episodes, hypopnea produces the same pathophysiological effects as apnea and thus the syndrome was renamed as OSAHS rather than OSA⁶.

OSAHS is defined as apnea-hypopnea index (AHI) ≥ 5 per hour. The severity can be judged based on the AHI as mild (AHI 5-15/h), moderate (AHI 15-30/h), and severe (AHI >30 /h)⁷. Patients of OSAHS are usually not hypercapnic when awake as they have a normal ventilatory drive; this is in contrast with Obesity Hypoventilation Syndrome (OHS) or Pickwickian syndrome where the patient usually has daytime hypercapnia due to a defect in ventilatory drive⁸.

NATURAL HISTORY OF OSAHS

Severity of OSAHS is known to worsen over time (roughly, AHI doubles every decade). This progression

is accelerated in obese individuals due to fatty infiltration of the upper airway soft tissue leading to further airway compromise⁶. Vibration induced trauma and edema of soft tissues of upper airways and pharyngeal muscle dysfunction are also responsible for progression of the disorder⁹. Over a period of time untreated OSAHS leads to pulmonary arterial hypertension, cor pulmonale, and hypercapnic respiratory failure¹.

CONSEQUENCES OF OSA

The adverse effects of the OSAHS are predominantly on the cardiovascular, neurologic and endocrine systems. The various effects are depicted in Table 1 and some of these are discussed below.

Table 1: Consequences of obstructive sleep apnea hypopnea syndrome

1. Cardiovascular	<ul style="list-style-type: none"> • Systemic hypertension • Coronary artery disease • Heart failure • Arrhythmias • Pulmonary hypertension • Cor pulmonale • Venous thromboembolism
2. Neurological	<ul style="list-style-type: none"> • Transient ischemic attacks • Ischemic stroke • Epilepsy • Cognitive dysfunction • Depression • Delirium
3. Endocrine	<ul style="list-style-type: none"> • Hypogonadism • Insulin resistance • Impotence • Erectile dysfunction
4. Miscellaneous	<ul style="list-style-type: none"> • Nocturia • Polycythemia • Esophageal reflux

Cardiovascular Consequences

Pathogenesis

The proposed mechanisms of adverse cardiovascular and cerebrovascular events are repeated bouts of hypoxemia, arousal from sleep, and large negative swings of intrathoracic pressure during the episodes³.

The intermittent hypoxemia followed by re-oxygenation is responsible for ischemia-reperfusion injury to the endothelium by generation of oxygen free radicals¹⁰. Hypoxemia thus causes endothelial dysfunction, platelet activation, expression of adhesion molecules and increased synthesis of coagulation factors. OSAHS causes accelerated atherosclerosis, thrombosis, and there is an increased occurrence of coronary artery disease and ischemic strokes.

Hypoxemia-induced chemoreceptor stimulation leads to intense sympathetic nervous system activation and elevated levels of circulating catecholamines, which lead to the development of sustained hypertension¹².

Large inspiratory swings of intrathoracic pressure contribute to increased venous return (preload) and increased left ventricular transmural pressure (afterload), thus precipitating left heart failure³.

Systemic Hypertension

There is evidence that OSA is etiologically important in the pathogenesis of sustained systemic hypertension. This relationship is strengthened by the dose dependence of hypertension with OSAHS severity. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (The JNC 7 Report) recommends considering OSAHS as an identifiable cause of hypertension¹³. OSAHS should also be considered in cases of refractory hypertension. Use of Continuous positive airway pressure (CPAP) for treatment of OSAHS reduces the blood pressure in patients with hypertension. Since the exact role of CPAP in treatment of hypertension in patients having hypertension with OSAHS is not clear as there is no data comparing CPAP with antihypertensive drug therapy, this aspect needs to be evaluated in prospective trials⁸.

Congestive Heart Failure (CHF)

The relationship of OSAHS with heart failure may be due to presence of common risk factors such as obesity, hypertension, CAD, and autonomic dysfunction. CHF may lead to new onset OSA in patients predisposed to upper airway closure by causing airway edema. Abnormalities in ventilatory drive in patients with CHF may lead to central sleep apnea and Cheyne-Stokes respiration. Treatment of OSAHS with nasal CPAP improves survival in systolic heart failure¹².

Coronary Artery Disease (CAD)

Accelerated atherosclerosis due to oxidative stress, pro-inflammatory mediators and growth factors such as endothelin and vascular endothelial growth factor

(VEGF) contributes to coronary artery disease. The Sleep Heart Health Study found OSAHS to be a modest independent risk factor for coronary artery disease and its severity predicted mortality in established CAD. CPAP therapy has been shown to relieve nocturnal angina and reduce the frequency of electrocardiographic abnormalities in patients with OSAHS and CAD¹⁴.

Cardiac Arrhythmias

The most common arrhythmias are severe sinus bradycardia, sinus arrest, and atrioventricular block due to reflex vagal stimulation due to apnea and hypoxemia. These arrhythmias respond readily to atropine¹². Tachyarrhythmias (ventricular ectopics, supraventricular tachycardia, and atrial fibrillation) are encountered less commonly in patients with OSAHS. Cardiac arrhythmias may be an important cause of deterioration with clinically significant comorbidities such as CAD or CHF. Sudden deaths due to ventricular arrhythmias or pump failure have also been reported. CPAP treatment reduces occurrence of arrhythmias in the subgroup of patients with CHF³.

Pulmonary Arterial Hypertension (PAH)

Apnea and hypoxemia are associated with acute elevations in pulmonary arterial pressure due to hypoxic pulmonary vasoconstriction. This is possibly due to elaboration of vasoactive substances from the endothelium. Chronic pulmonary hypertension results from endothelial damage and vascular remodeling due to elaboration of VEGF and other mediators. But the presence of other confounding factors such as CAD, heart failure and obesity make the association of OSAHS with PAH difficult to establish^{8,12}.

Venous Thromboembolism (VTE)

OSAHS predispose to VTE due to alterations in coagulation factors, platelet activation, endothelial damage and presence of comorbidities such as hypertension, CAD, CHF and obesity. Prospective studies are needed before 'cause and effect' relationship can be confirmed⁸.

Neurologic Effects

Stroke and TIA

Sleep disordered breathing is associated with increased risk of stroke and transient ischemic attacks independent of the other risk factors. Various factors including reduced cerebral blood flow, altered cerebral auto-regulation, accelerated atherosclerosis, thrombosis,

and rarely paradoxical embolism through patent foramen ovale are incriminated. The presence of systemic hypertension plays a major role in increasing the risk of stroke in OSAHS. In addition, the presence of OSAHS is associated with unfavorable outcome after stroke and poor functional status after recovery from the stroke¹⁵.

Epilepsy

Sleep disorders frequently coexist with epilepsy and seizure disorders by themselves can lead to sleep disturbance. Drowsiness in refractory epilepsy must not be ascribed to the side-effects of antiepileptic medication, but should be evaluated by polysomnography and video EEG for underlying cause. The diagnosis and treatment of OSAHS would lead to better seizure control and sleep architecture, and quality of life¹⁶.

Endocrine Effects

Hypogonadism

Exogenous androgen therapy is known to exacerbate OSAHS whereas hormone replacement therapy in menopausal women is protective. OSAHS has adverse effects on testicular function through suppression of pituitary gonadal axis and CPAP reverses the OSAHS associated hypogonadism. But whether CPAP improves ovarian function in women has not been evaluated⁸.

Insulin Resistance

OSAHS is common in Diabetes Mellitus, and both are co-associated with obesity. Insulin resistance and hyperinsulinemia are associated with central obesity and OSHAS aggravates the situation due to increased adrenergic hormones, hypoxemia-induced glucose dysregulation, and effect of proinflammatory cytokines. The effect of CPAP on glucose metabolism and insulin resistance has been more pronounced in non-obese OSAHS patients suggesting that insulin resistance in obese individuals is mainly due to obesity and lesser extent OSAHS¹⁷.

CONCLUSIONS

Patients with OSAHS may present to the sleep clinic or to various other specialty clinics with non-specific complaints. A high index of suspicion needs to be maintained in order to diagnose these atypical presentations. The syndrome produces profound cardiovascular, neurological, and endocrinological effects which are responsible for the morbidity and mortality. By the application of effective treatment strategy of nasal CPAP,

most of the adverse consequences can be minimized or averted.

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