NAMSCON 2013

53rd Annual Conference
of
National Academy of Medical Sciences (India)

25th- 27th October 2013

All India Institute of Medical Sciences
Jodhpur

National Academy of Medical Sciences
New Delhi

NAMS Regional Symposium
on
Sleep Medicine

25th October, 2013

Handbook of Learning Resource Material

All India Institute of Medical Sciences
Jodhpur - 342005, Rajasthan, India

NAMSCON 2013

53rd Annual Conference
of
National Academy of Medical Sciences (India)

25th- 27th October 2013

NAMS Regional Symposium on Sleep Medicine

25th October 2013

Handbook Of Learning Resource Material

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR

CONTENTS

NAMS Regional Symposium on Sleep Medicine
Speaker : ***Dr. V. Mohan Kumar***

PHYSIOLOGY OF NORMAL SLEEP: FROM YOUNG TO OLD

SYNOPSIS

Behaviourally, sleep is characterised by reduced motor activity, decreased response to stimulation, stereotyped posture and relatively easy reversibility. Scientifically, sleep is defined on the basis of electrophysiological signals like electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG). Though modern definition and classification of sleep was suggested by Nathaniel Kleitman in 1939, it is described in detail in a manual written by Rechtschaffen and Kales[1]. Normal human sleep was divided into non–rapid eye movement (NREM) sleep (four stages) and REM sleep. The American Academy of Sleep Medicine slightly modified the staging rules in 2007[2].

Sleep starts with a period of NREM sleep. REM sleep takes place after a short period of NREM sleep. This alteration between NREM and REM occurs about 4-5 times during a normal night's sleep. As NREM sleep progresses to deeper stages, the EEG shows increasing voltage and decreasing frequency. Though muscle activity is progressively reduced, the sleeper makes postural adjustments after about every 20 minutes. During NREM sleep the heart rate and BP decline, but the gastrointestinal motility and parasympathetic activity increase. On the other hand, REM sleep is characterised by a profound loss of muscle tone, though the eyeballs show bursts of rapid eye movements. The EEG becomes desynchronised during this phase.

Circadian sleep-wake rhythm with periodicity in physiological, biochemical, and psychological processes is modulated by the suprachiasmatic nucleus of the hypothalamus, and the pineal gland. These brain areas set the body clock periodicity to approximately 25 hours, but with environmental clues (like light exposure) and activity schedule, the sleep-wake rhythm is entrained to a 24-hour cycle.

Newborns show several sleep-wake cycles in a day of 24 hours. This polycyclic rhythm passes through a biphasic pattern before a monocyclic pattern is established in young adults. In newborns, the total duration of sleep in a day can be 14-16 hours. Most of it is REM sleep. In adults, sleep of 7-8.5 hours is considered fully restorative. The amount of sleep needed by each person is usually constant, although there is a wide variation among individuals. During old age, total sleep is not only reduced, it is often divided into an overnight sleep period of less than 6-7.5 hours and a midafternoon nap of about one hour. This biphasic sleep pattern is also observed in young adults in some cultures.

Sleep was considered as a passive process till the 1950's. This passive theory of sleep was replaced by the active sleep genesis concept, mainly after the realization that brain activity is only slightly reduced during sleep. There is now growing evidence to suggest that sleep is auto-regulatory and that it is not necessary to attribute sleep genesis to either an active or a passive mechanism[3,4].

Sleep is considered essential for life[5]. It may be having a restorative and recovery function, especially for the brain. Energy conservation could be one function of sleep. The role of REM sleep in brain growth has been suggested for long. Sleep may also facilitate neurogenesis. Memory consolidation during sleep has been proposed by many investigators. Discharge of emotions through dreaming is an age-old function ascribed to sleep. Sleep may have a thermoregulatory function.

The importance of sleep is evident from the health problems resulting from sleep disorders. Some sleep disturbances can be described as temporary mild inconveniences, while others are far more serious with disastrous consequences. Persistent and repeated interruption of sleep affects the physical and mental health of the individual. Inadequate sleep causes not only misery to the sufferer, but it also has far reaching socioeconomic consequences.

SUGGESTED READING

1. Rechtschaffen A and Kales AA. A manual of Standardized Terminology: Technique and Scoring Systems for Sleep Stages of Human Subjects. National Institutes of Neurological Diseases and Blindness, Bethesda, MD, 1968: 1–57.
2. Iber C, Ancoli-Israel S, Chesson AL, and Quan SF. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications. Westchester, Ill: American Academy of Sleep Medicine; 2007.
3. KumarVM (2010).Sleep is neither a passive nor an active phenomenon. Sleep and Biological Rhythms8: 163–169.

NAMS Regional Symposium on Sleep Medicine
Speaker : ***Dr. K.K. Sharma***

PHARMACOLOGY OF SLEEP

SYNOPSIS

Sleep is an altered state of consciousness necessary for the well being of an organism. It is estimated that humans spend approximately one-third of their lives in sleep. Humans deprived of sleep for long periods become emotionally disturbed and may manifest a number of medical problems including disturbed cardiovascular, metabolic, cognitive and psychiatric functions.

Based on three physiological measurements (EEG, EOG and EMG), sleep is divided into two states with independent functions and controls: Non Rapid Eye Movement (NREM) and REM sleep, alternating in a cyclic manner. NREM sleep (also known as synchronized sleep, light sleep, slow- wave sleep) constitutes 75-80% of the sleeping period in adults. NREM sleep is sub-divided into 4 stages (I to IV) according to the traditional Rechtschaffen and Kales (R-K) scoring manual. But, according to the recent American Academy of Sleep Medicine (AASM) scoring system, this is sub-divided into 3 stages (N1, N2, N3), mainly on the basis of EEG criteria. REM sleep (also known as desynchronized sleep, deep sleep, paradoxical sleep, dreaming sleep, fast -wave sleep) constitutes 20-25% of sleeping time in adults.
Neurochemical Circuitry Involved in Wake-Sleep Cycle:
Many neurochemical systems interact to generate wakefulness and sleep. Wakefulness is promoted by neurons in the pons, midbrain, and posterior hypothalamus that produce acetylcholine, norepinephrine, dopamine, serotonin, histamine and orexin/hypocretin. Most of these ascending arousal systems cause low-voltage, fast activity in the EEG and diffusely activate the cortex and other forebrain targets. NREM sleep is mainly driven by neurons in the pre-optic area that inhibit the ascending arousal systems (mainly through the inhibitory neurotransmitters GABA and neuropeptide galanin, which produce large amplitude, slow EEG oscillations), while REM sleep is regulated primarily by neurons in the pons, with additional influence arising in the (lateral) hypothalamus by using neurotransmitters like acetylcholine, monoamines, GABA and Melanin-Concentrating Hormone (MCH). Mutual inhibition between these wake-and sleep-regulating regions likely helps generate full wakefulness and sleep with rapid transitions between these states. Some homeostatic sleep factors, called somnogens (to name a few: adenosine, cytokines: IL-1 , TNF- , prostaglandin PGD2 and nitric oxide) mainly produced during prolonged wakeful state also affect and modify the NREM and REM sleep.

NREM sleep results in conservation of brain energy and facilitates memory consolidation through the modulation of synaptic mechanisms. REM sleep phenomena such as muscle atonia, dreaming, and cortical activation occur as a result of interaction of inhibitory neurotransmitters (Ach, monoamines GABA, MCH) with glutamatergic reticular formation neurons that project to both limbic regions and the spinal cord. A disruption of sleep interferes with the normal restorative functions of NREM and REM sleep, resulting in altered breathing and cardiovascular functions, changes in emotional reactivity, and cognitive impairments in attention, memory and decision making. A broad understanding of all neurotransmitter mechanisms involved in wake-sleep cycle allow clinicians and researchers to better understand the effects of drugs, lesions, and neurologic diseases of sleep and wakefulness.
Pharmacology of Drugs used in Sleep Disorders:
Given the high prevalence of sleep disorders in the general population and in patients with a variety of co-morbid ailments and disorders, the pharmacological treatment options for sleep disorders are common considerations for sleep specialists and non-specialists alike. Clinical pharmacology of sleep medicine can be loosely classified into drugs aimed at treating:-
- Sleepiness (Hypersomnias),
- Sleeplessness, and
- Sleep-related movement disturbances.
Although most of the drugs are available by prescription only, the stimulant caffeine and the antihistamine, diphenhydramine are common over-the-counter options for sleepiness and sleeplessness, respectively.
The primary hypersomnias are uncommon compared to disorders that include sleepiness as a

Cont....

secondary symptom to sleep disruption. When presented with the patient reporting sleepiness, it is critical to investigate potential primary causes, such as sleep apnea or insomnia. Pain syndromes, mood disorders and general medical problems may be co-morbid with sleep apnea and/or disrupted sleep. However, residual day-time

symptoms persist in some patients despite optimized management of potential primary causes, leading to consideration of stimulant agents in the appropriate clinical setting. Primary hypersomnias such as narcolepsy – cataplexy syndrome and idiopathic hypersomnia are also treated primarily with the use of stimulants acting on the dopaminergic systems (e.g., modafinil) to alleviate excessive daytime sleepiness and antidepressants [especially those promoting increased noradrenergic tone: amitriptyline, protriptyline with or without gamma-Hydroxybutyrate (GHB, sodium oxybate) are prescribed to improve night-time sleep in narcoleptics]. GHB is a metabolite of GABA that modulates sleep via activation of GABA B receptors. Newer therapies which include pharmacological agonists of the orexin receptor antagonists (almorexant, MK-4305) and histamine H3 receptor antagonists/inverse agonists (pitolisant) are under development for the treatment of narcolepsy.

Insomnia can be considered a constellation of symptoms with a variety of underlying causes. As a symptom, it can be secondary to disorders of mood, pain, or a variety of other neurological and general medical disorders. It can be primary in the sense that it exists in the absence of other identifiable causes, such as insomnia from psychophysiological associations, or secondary to a number of other medical and psychiatric problems. One of the most intriguing, yet poorly understood aspects of insomnia, is the misperception phenotype, in which patients underestimate their sleep times compared to objective measurements. Insomnia can also be the presenting feature of circadian phase disorders – most commonly, delayed circadian phase. The primary challenge with regards to the diagnosis and treatment of insomnia is that both depend entirely on the clinical history, with no basis in objective testing.

Pharmacological treatment of insomnia usually involves sleep aids, e.g.: 1. Drugs acting as agonists of the -1 subunit of the GABA receptor, such as benzodiazepines and the "Z" drugs (zollpidem, zalpelon, zopiclone) which potentiate the action of sleep-promoting GABAnergic neurons; 2. Melatonin and melatonin receptor agonist ramelteon; 3. Ritanserin, an antagonist of both 5-HT2A and 5-HT2C receptors; and 4. Antidepressants such as trazadone and agomelatine, a unique compound that acts as both a serotonergic 5-HT2C antagonist and melatonin receptor agonist. A variety of other compounds used to treat insomnia antagonize histaminergic and orexinergic wake-promoting nuclei (almorexant and MK-4305), were shown to enhance both NREM and REM sleep and reduce wakefulness in animals, healthy humans and insomniacs.

Restless leg syndrome and periodic limb movements of sleep are the most common movement disorders resulting in sleep disturbance. The former is a strictly clinical diagnosis while the latter is a polysomnographic finding. Both are treated similarly, often beginning with interrogation of iron stores and oral repletion when needed, followed by dopaminergic medications (pramipexole, ropinirole), as well as off-label use of other classes of agents. REM behavior disorder (RBD) is most commonly treated with hypnotic benzodiazepines.

SUGGESTED READING

1. **Chokroverty S (2010). Overview of sleep & sleep disorders.** *Indian J Med Res.* **131:126-140.**
2. **Espana RA (2011). Scammell TE. Sleep neurobiology from a Clinical Perspective.** *Sleep*. **34 (7): 845-858.**

NAMS Regional Symposium on Sleep Medicine
Speaker : ***Dr. Naveen Dutt***

OBSTRUCTIVE SLEEP APNEA AND QUALITY OF LIFE

SYNOPSIS

Obstructive sleep apnea (OSA) is characterized by the occurrence of daytime sleepiness, loud snoring, breathing interruptions, or awakenings due to gasping or choking in the presence of at least five obstructive respiratory events (apneas, hypopneas or respiratory effort related arousals) per hour of sleep. The presence of 15 or more obstructive respiratory events per hour of sleep in the absence of sleep related symptoms is also sufficient for the diagnosis of OSA due to the greater association of this severity of obstruction with important consequences such as increased cardiovascular disease risk. Prevalence surveys have estimated that about 4% of the middle-aged men and 2% of the middle-aged women are afflicted by OSA in developed countries(1). Indian prevalence studies estimated disease prevalence rates of 3.5-13.7% (4.4-19.5% in males and 2.5-7.4% in females) prevalence of OSAS in India is 1.7-3.6% (2.4-7.5% in males and 1-2.1% in females).

The daytime sleepiness is the most common manifestation of OSA. However, other common daytime effects include irritability, decreased concentration, memory impairment, decreased energy and depressive symptom. The most catastrophic result of excessive daytime sleepiness (EDS) is falling asleep behind the wheel and causing fatal automobile accidents. Many studies have indicated an association between sleep apnea and cardiovascular/cerebrovascular related morbidity and mortality. It has been associated with the hypertension, coronary artery disease, congestive heart failure, arrhythmias and stroke. It has also been associated with an increased mortality.

Recently, the studies have confirmed that the impact of OSA on patient's quality of life (QOL) is rather more widespread than EDS, increased risk of cerebrovascular/cardiovascular events and other common features mentioned above. Certainly, there are many other domains of life, which remain unexplored in the sleep laboratory. In such cases, Flemons and Lacasse et al. have outlined 4 such key domains of health related quality of life (HRQoL) viz. somatic sensation, physical function, emotional state, and social interaction(2). As the measurements of physiological parameters alone cannot be taken surrogate markers of HRQoL this emphasizes the need to measure QOL directly.

Diverse self-reported instruments have been used to assess resulting impairment like medical outcomes study survey, Short-form 36 health survey Questionnaire (SF-36), Satisfaction with Life Scale, Nottingham Health Profile, General health questionnaire-28(3).

Question mark on the ability of generic questionnaire to detect subtle effects of disease on QOL and effects on QOL brought about by various treatment modalities led to the development of disease specific questionnaire for OSA like Calgary sleep apnea quality of life index (SAQLI) functional outcome of sleepiness questionnaire (FOSQ), and OSA Patient-Oriented Severity Index(4)(5). These OSA specific questionnaires are being used increasingly in the newer studies and gradually replacing the generic scales.

It is essential to study the overall effect of OSA on human life so that a complete therapy can be planned addressing the specific needs of the patient. Any treatment modality chosen on the basis of derangements in the physiological parameters only is unlikely to be complete as these parameters may not be the true representative of the extent of suffering of the OSA patients.

SUGGESTED READING

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S (1993). The occurrence of sleep-disordered breathing among middle-aged adults. *N. Engl. J. Med.* **328 :1230–5.**

2. Flemons WW, Reimer MA. Development of a disease-specific health-related quality of life questionnaire for sleep apnea (1998). *Am. J. Respir. Crit. Care Med.* **158:494–503.**

3. Goncalves MA, Paiva T, Ramos E, Guilleminault C (2004). Obstructive sleep apnea syndrome, sleepiness,

NAMS Regional Symposium on Sleep Medicine
Speaker : ***Dr. V.K. Vijayan***

SLEEP DISORDERED BREATHING: OBSTRUCTIVE SLEEP APNEA, CENTRAL SLEEP APNEA - PATHOPHYSIOLOGY AND DIAGNOSIS

SYNOPSIS

The obstructive sleep apnea (OSA) is the repetitive interruption of ventilation during sleep caused by collapse of the pharyngeal airway and the central sleep apnea (CSA) is the repetitive cessation of ventilation during sleep resulting from loss of ventilatory drive. OSA is defined as cessation of airflow > 10 seconds despite continuing ventilatory effort with five or more such episodes per hour of sleep and is usually associated with a decrease of > 4% in oxyhemoglobin saturation. Hypopnea is characterized by a reduction of > 50% in airflow for > 10 seconds associated with a > 3% decrease in oxygen saturation and/or arousal. The obstructive sleep apnea syndrome (OSAS) defined as OSA associated with excessive daytime sleepiness, affects 2 to 4% of middle-aged adults. Risk factors for development of OSA are classified as non-modifiable and modifiable factors. The important non-modifiable risk factors are age, male gender, anatomical abnormalities of craniofacial regions and upper airway, thick neck with circumference more than 17 inches and a genetic predisposition. The important modifiable risk factors are obesity, use of alcohol or sedatives, narrowed airways due to enlarged tonsils or adenoids, smoking, chronic nasal congestion, myxedema and menopause. OSA-induced biological changes include intermittent hypoxia, intermittent hypercapnia, intra thoracic pressure changes, and sympathetic activation and sleep fragmentation. These biological changes lead to oxidative stress, systemic inflammation, metabolic dysregulation, and hypercoagulation and neurohumoral changes. Studies had demonstrated that there was an increase in thiobarbituric acid-reactive (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. A marked increase in TNF- and CD40 ligand in CD8 T cells was reported. Increased circulating levels of CRP have been consistently reported in both adults as well as in children. 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. 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. Recurrent hypoxemia has been found to increase the endothelin levels in OSA and there is a reduction in endothelin levels on treatment with OSA. Endothelin is a potent vasoconstrictor which causes elevated blood pressure.There are elevated levels of plasma fibrinogen, exaggerated platelet activity and reduced fibrinolytic activity suggesting that there is a hypercoagulable state. The repetitive inspiratory efforts against a closed upper airway observed in OSA lead to increased negative intrathoracic pressure resulting in an increase in transmural gradients across the atria, ventricles and aorta. These changes in transmural gradients can result in autonomic and hemodynamic instability. The cardinal features of OSA are loud snoring andexcessive daytime sleepiness. The assessment of sleepiness can be done with Epworth sleepiness scale orStanford sleepiness scale. The gold standard for diagnosis of OSA is polysomnography in which there is simultaneous monitoring of nasal and/or oral airflow, thoracoabdominal movement, electroencephalogram, electro-oculogram, and electromyogram and oxygen saturation.

SUGGESTED READING

1. Iber C, Ancoli-Israel S, Chesson AL Jr, Quan SF, for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.

2. Young T, Skatrud J. Peppard PE (2004). Risk factors for obstructive sleep apnea in adults. *JAMA* **291: 2013-6.**

NAMS Regional Symposium on Sleep Medicine
Speaker : ***Dr.Ravinder Goswami***

ENDOCRINE AND METABOLIC ASPECTS OF OSA

SYNOPSIS

Obstructive sleep apnoea (OSA) is a clinical disorder characterized by repeated spells of apnoea (lasting at least 10 seconds) interspersed with episodes of hypopnea (reduction in inspiratory flow of at least 50% for 10 sec and fall in O2 saturation of 4%). The increased collapsibility of hypopharynx due to multiple factors including deposition of fat or fluid in the surrounding soft tissue are important contributing factors. The disorder commonly affects obese individuals but can also be seen in non-obese subjects. Males are more commonly affected than the females due to disturbing effect of testosterone on sleep. Since estrogen has protective effect the skewed predisposition is decreased following menopause.

The narrowing of the hypopharynx translates into snoring due to fluttering of the uvula and frequent arousal in the night. Presently, sleep polysomnography is the ideal method to diagnose the disease with Apnoea/Hypopnea index (AHI) > 15 being characteristic of the OSA. The fragmentation of sleep leads to day time sleepiness and associated neuro-cognitive disturbances and cardiovascular morbidity and mortality.

The multiple ramifications of OSA on human health include several disturbances in Endocrine and Metabolic system affecting hypothalamic-pituitary-gonadal axis, adrenocorticotrophic and cortisol axis, growth hormone, antidiuretic hormone and degree of insulin resistance. There is a tendency for predisposition to metabolic syndrome or its various components including glycemic disturbances, hypertension , dyslipidemia and visceral adiposity. On the other hand several primary endocrine disorders such as hypothyroidism, growth hormone excess either due to acromegaly or during therapy for growth hormone deficiency, testosterone replacement and polycystic ovarian disease are associated with increased prevalence of metabolic syndrome.

Most of the information associating OSA with above mentioned endocrine disturbances is based on observational studies. There is limited information on the effect of treatment of OSA by continuous positive airway pressure (CPAP) on the endocrine and metabolic disturbances. Thus, there is urgent need to conduct randomized trials using CPAP in patients with OSD and endocrine and metabolic disturbances to study the cause and effect relationship.

SUGGESTED READING

1. Attal P, Chanson P (2010). Endocrine aspects of obstructive sleep apnea. *J Clin Endocrino Metab*.**95:483-95.**

2 .Kamenov Z, Gateva A, Hihashino H, Angelova P and Georgiev (2010). Endocrine aspects of obstructive sleep apnea. *Acta Med Kinki Univ***35 : 67-75.**

3. Reutrakul S, Zaidi N, Wroblewski K, Kay HH, Ismail M, Ehrmann DA, Van Cauter E. Interactions Between Pregnancy, Obstructive Sleep Apnea, and Gestational Diabetes Mellitus. *J ClinEndocrinolMetab*. **2013 Aug 21. [Epub ahead of print] PubMed PMID: 23966237.**

NAMS Regional Symposium on Sleep Medicine
Speaker : ***Dr. V.K. Vijayan***

CO-MORBIDITIES ASSOCIATED WITH OBSTRUCTIVE SLEEP APNEA

SYNOPSIS

Obstructive sleep apnea (OSA) has been shown to increase the risk for systemic hypertension, pulmonary vascular disease, ischemic heart disease, cerebral vascular disease, congestive heart failure and arrhythmias. However, a causal relationship is difficult to establish as many risk factors of OSA are also known risk factors of cardiovascular diseases. Several studies have shown that OSA increases the relative risk of hypertension independent of other confounding factors. The Wisconsin sleep cohort study had demonstrated a dose-response association between sleep disordered breathing at baseline and the presence of hypertension four years later and this was independent of known confounding factors.Sleep Heart Health Study (SHHS) in a cross sectional analysis of > 6000 patients has shown a linear relationship between systolic and diastolic blood pressure and OSA severity.In another prospective study of 2470 participants of SHHS aged > 40 years without baseline hypertension and not on antihypertensive medication, it has been shown that there is a significant relationship between the risk of developing hypertension and OSA. However, this association was lost after adjustment for BMI. In a longitudinal study in the general population (Victoria Sleep Cohort) involving 2148 subjects and with a 7.5-year follow up, there is no suggestion of an association between OSA and incident systemic hypertension in the middle aged general population. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-VII) lists sleep apnea as a significant cause of secondary hypertension. Case series studies mainly in male patients have suggested that the prevalence of pulmonary hypertension in OSA varies from 17 to 53%. However, there are no population based data to know the prevalence of pulmonary hypertension in OSA. The prevalence of cardiac arrhythmias from the Sleep Heart Health study showed that severe OSA had higher rates of atrial fibrillation, non-sustained ventricular tachycardia and complex ventricular ectopy. Observational studies had shown that severe obstructive sleep apnea-hypopnea significantly increased the risk of fatal and non-fatal cardiovascular events in both men and women and CPAP treatment reduced this risk. The Framingham study had shown that increasing BMI is directly correlated with incident heart failure and may be mediated in part by OSA. There are evidences suggesting that OSA is independently associated with metabolic syndrome. The Wisconsin Sleep Cohort had demonstrated that moderate to severe sleep-disordered breathing is a risk factor for prevalent stroke. It has been observed that sleep capnea occurs frequently after stroke and CPAP treatment has been found to improve neurological recovery after stroke.It has been reported that there is a high prevalence of erectile dysfunction in OSA patients. It was observed that abdominal aortic aneurysm is highly prevalent in OSA and there was further expansion of abdominal aortic aneurysm in patients with severe OSA. Sleep-disordered breathing was also found to be associated with deep vein thrombosis and pulmonary embolism in female patients with OSA and this association was independent of established risk factors for thrombosis. Neurocognitive consequences of OSA include daytime sleepiness, loss of alertness, memory deficit, reduced vigilance, impaired executive function, psychomotor speed deficits, increased risk for automobile and occupational accidents and decreased quality of life.

SUGGESTED READING

1. **American Heart Association/American College of Cardiology Foundation Scientific Statement: Sleep a p n e a and cardiovascular disease.** *Circulation* **2008; 118:1080-1111.**
2. **Vijayan VK (2012). Morbidities associated with obstructive sleep apnea.***Expert Rev Respir Med.* **6:557-66.**
3. **Lam JCM, Mak JCW and Ip MS (2012). Obesity, obstructive sleep apnea and metabolic syndrome.** *Respirology* **17: 223–236.**

NAMS Regional Symposium on Sleep Medicine
Speaker : ***Dr. Rajeshwar Dayal***

CHILDHOOD OBSTRUCTIVE SLEEP APNEA

SYNOPSIS

Sleep apnea forms a part of the spectrum of sleep disordered breathing. It may be Central, Obstructive or of the Mixed Variety.

Obstructive Sleep Apnea is a sleep disorder characterized by recurrent episodes of narrowing or collapse of pharyngeal airway during sleep despite ongoing breathing efforts. It's incidence varies from 1-3% in children of preschool age in most western studies. Very few studies have been conducted in our country. In an Indian study among urban pre-school children, the incidence was found to be 4.7% of all sleep disorders (Suri et al,2008).

Upper airway obstruction can be either partial (Snoring) or Complete (OSA). This leads to decreased alveolar ventilation, decreased alveolar& arterial PO2 and increased PCO2 which stimulates arterial chemoreceptor's leading to arousal/ partial awakening. Obstruction occurs during supine position due to lack of "wakefulness" drive, decreased tone of pharyngeal muscles, intercostals and accessory muscle and depressed reflexes, minute volume and response to hypoxia.

Various anatomic factors (e.g. adenotonsillar hypertrophy) and functional factors (e.g. obesity) cause OSA .

The classic presentation of children with OSAS as underweight children with adenotonsillar hypertrophy is being substantially replaced by young patients who are either overweight or obese. In obese, upper airway narrowing results from fatty infiltration of upper airway structures promoting pharyngeal collapsibility. Obesity reduce the intrathoracic volume and diaphragmatic descent during inspiration, particularly in the supine position, resulting in lower oxygen reserves and increased work of breathing during sleep which decrease airway stiffness. Obesity also results in blunted ventilatory responses to hypoxia and hypercapnia. Further, reduced bioavailability of leptin (an adipocyte derived hormone) resulting in altered ventilatory responses may also play a role in the interaction between obesity and OSAS.

Clinically, the patient may present with sleep related symptoms (e.g.snoring, breathing pauses, choking or gasping arousal, restless sleep, nocturnal diaphoresis, enuresis) ,daytime symptoms (e.g. morning headaches, excessive daytime sleepiness, dry mouth, chronic mouth breathing ,poor appetite and failure to thrive) and neurobehavioural symptoms (e.g. .deficits in attention, memory deficits, mood disturbance, subjective sleepiness, poor school performance) Typically, no respiratory abnormality occurs while the child is awake. In longstanding cases, patient may develop systemic or pulmonary hypertension, polycythemia, corpulmonale and bradycardia.

The gold standard diagnostic test is polysomnography. Treatment modalities range from lifestyle modifications, pharmacological treatment like topical nasal steroids (for nasal obstruction) steroids & antibiotics (infected pharyngeal tissue) and nasal decongestants (for allergic rhinitis) to surgical therapies.

NAMS Regional Symposium on Sleep Medicine
Speaker : ***Dr. V.K. Vijayan***

TREATMENT OF OBSTRUCTIVE SLEEP APNEA

SYNOPSIS

The non-surgical conservative treatment of OSA includes weight reduction, avoidance of alcohol for 4-6 hours prior to bedtime, and sleeping on one's side rather than on the back. 10% reduction in weight has been shown to lead to a 26% reduction in the respiratory disturbance index (RDI). Continuous Positive Airway Pressure (CPAP) is recommended as the first-line therapy for severe obstructive sleep apnea and for OSA associated with cardiovascular disorders. CPAP which acts physiologically as a pneumatic splint maintains a constant pressurein the upper airway throughout the respiratorycycle.CPAP is recommended for patients with symptomaticobstructive sleep apnea even if the apnea–hypopnea index is in the mild range (5 to 15). The relative contraindications to the use of CPAP are bullous lung disease and recurrent sinus or ear infections. CPAP treatment has been found to reduce the cognitive impairment and sleepiness associated with OSA in randomised controlled trials. Some randomized trials, but not in others, had also shown that CPAP reduced blood pressure in both hypertensive and normotensive patients with OSA. The pressure that has to be prescribed for CPAP treatment is titrated during polysomnography. This enables to find the minimal and optimal level of CPAP that is required to ameliorate the obstructive events, restore normal levels of arterial oxygen saturation and decrease the frequency of arousals in all positions and stages of sleep. Adherence to CPAP treatment is a problem in OSA. Patients have been considered compliant if they use their CPAP device more than 4 hours per night, 5-7 nights per week. It has been reported that 20-40% of patients do not use the prescribed CPAP therapy. Conventional fixed-pressure CPAP delivers a fixed airway pressure and is effective in most patients. However, other modes of pressure delivery such as bilevel positive airway pressure, auto-adjusted CPAP, and pressure-relief CPAP are also available. Other mechanical devices for treatment include Bilevel positive airway pressure (BiPAP) and oral appliances (OA). Oral Appliances act by pulling the tongue forward or by moving the mandible and soft palate anteriorly and this enlarges the posterior airspace and helps to open or dilate the airway. Currently, three basic designs of OAs that can be used to treat sleep-related breathing disorders are mandibular repositioners, tongue-retaining devices (TRDs), and palatal-lifting devices. There are no convincing evidences that these alternate devices are better than the conventional fixed-pressure CPAP with regard to compliance or efficacy. Surgical correction of the upper airway is indicated in patients who have a specific underlying abnormality that is causing the OSA. Surgical removal of enlarged adenoids and tonsils are practiced if these are found to be the cause for OSA especially in children. Uvulopalatopharyngoplasty, uvulopalatal flap and RF ablation of the soft palate are some of the important surgical procedures that may help to reduce soft palate redundancy. Pharmacologic therapy is not the primary form of treatment in OSA. There are no clinically useful drugs for treatment of OSA, except in certain cases of residual sleepiness persisting despite apparently successful treatment. Modafinil is the drug used for this purpose. Medical conditions that may cause OSA such as myxedema and gigantism can be treated with specific therapy.

SUGGESTED READING

1. Basner RC (2007).Continuous Positive Airway Pressurefor Obstructive Sleep Apnea. *N Engl J Med* **356:1751-80.**

2. Epstein LJ, Kristo D, Strollo PJ et al. (2009). Guidelines for the evaluation, management and long-term care of obstructive sleep apnea in adults: Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* **5: 263-276.**

3. Collop NA, Anderson WM, Boehlecke B et al. (2007). Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the

NAMS Regional Symposium on Sleep Medicine
Speaker : **Dr. M.V. Padma Srivastava**

OBSTRUCTIVE SLEEP APNOEA (OSA) AND STROKE

SYNOPSIS

Evidence is growing that not only is obstructive sleep apnoea (OSA) an independent risk factor for stroke, but that treating OSA improves recovery from stroke. However, unlike aggressive treatment of conventional risk factors for stroke, such as hypertension, atrial fibrillation, hypercholesterolemia and carotid stenosis, OSA is overlooked. Without understanding the link between OSA and stroke, whether the relationship is just an association or actually causal, and the pathophysiological mechanisms connecting the two, an important opportunity of intervening with evidence-based, well directed stroke preventive and therapeutic option is being missed. OSA has often been documented in cohorts recovering from recent stroke, which begs the questions of whether stroke leads to OSA or if OSA causes stroke, or if the relationship between OSA and stroke is bidirectional.

In a study unattended overnight PSG (Polysomnography) was performed at home in a cohort of 6424 individuals. Significantly, the result showed that not only was there a positive association between the severity of OSA, as measured by the Apnoea-Hypopnoea Index (AHI), and the risk developing cardiovascular events, including stroke, but that even mild to moderate OSA was detrimental-independent of other known risk factors.

The initial suspicion of a link between Sleep Disordered Breathing (SDB) and stroke was raised through epidemiological studies first conducted in 1980-1990s. Strength of association between stroke and snoring equaled other traditional stroke risk factors and held true independently, even when adjusted for confounding risk factors such as hypertension, smoking, atrial fibrillation and hypercholesterolemia.But temporal relationship between snoring and stroke has not been established because snoring, similar to OSA, can well be a consequence of stroke rather than causing it.

The reported frequency of OSA in stroke patients varies between 30% and 80%. In recent meta- analysis of ischemic or hemorrhagic stroke and transient ischemic attack (TIA) patients, the frequency of SDB with AHI of >5 was 72 %, and with an AHI of >20 was 38%, it was reconfirmed by a previously reported higher prevalence of SDB (AHI>10) in men compared with women (65% vs. 48%; p-0.001), and also a higher percentage of SDB (AHI>10) in patients with recurrent stroke than initial stroke (74% vs. 57%; p-0.013). Patients with cardio embolic strokes had a lower percentage of SDB compared with patients with strokes due to unknown etiologies.

Various studies also support causal association between hypertension and OSA. Sleep heart health study demonstrated that sustained diurnal hypertension is a consequence of chronic OSA. The relative risk of hypertension in severe OSA (AHI>30) compared with the mildest category (AHI < 1.5) in this study was 1.37 (95%, CI: 1.03-1.83), and the odds for hypertension increased with AHI in a dose-response manner. Treatment of OSA with CPAP (Continuous Positive Airway Pressure), compared to sham CPAP, reduced the severity of hypertension, which further supports an association between OSA and hypertension. OSA may raise the systemic blood pressure significantly and thus can be one of the most important mechanism by which OSA leads to cerebrovascular morbidity.

Mechanism of interaction between OSA and normal blood pressure leading to hypertension has been studied and it is observed that patients with OSA have considerably higher sympathetic activity compared with controls, even during wakefulness. A modification caused in renal physiology in the form of an augmentation of the rennin-angiotensin system in face of chronic OSA-induced hypoxia has also been postulated as an explanation for the genesis of hypertension in OSA. OSA is also been implicated in contributing to drug resistant hypertension.

In conclusion, OSA is a modifiable risk factor for stroke. Whether every patient with stroke should be screened for OSA and whether treatment for OSA should commence during the acute stroke or stroke rehabilitation, or as a primary or secondary prevention tool, is presently unclear. Given that OSA is associated consistently with an increased risk of stroke, and recovery from stroke is worse in patients with OSA, there seems to be a compelling case to conduct randomized trials of CPAP therapy for prevention of major cardiovascular events including stroke, in patients with OSA.

SUGGESTED READING

1. Partinen M, palomaki H (1985). Snoring and cerebral infarction. *Lancet* **2:1325-6.**

2. Basstti C, Aldrich M, chervin R et al(1996). Sleep apnea in patients with transient ischemic attack and stroke:
A prospective study of 59 patients. *Neurology* **47:1167-73.**

NAMS Regional Symposium on Sleep Medicine
Speaker : ***Dr.K.Radhakrishnan***

SLEEP IN EPILEPSY

NAMS Regional Symposium on Sleep Medicine
Speaker : ***Dr. M.V. Padma Srivastava***

CAUSES OF HYPERSOMNIA – NARCOLEPSY

SYNOPSIS

Volitional sleep deprivation and obstructive sleep apnea are the most common causes of hypersomnia. The remaining causes are primarily due to primary central nervous system abnormalities, the most common of which is narcolepsy, a primary disorder of the neural control of wakefulness and sleep.

Narcolepsy is the prototypic example of dissociated sleep-wake phenomenon in which components of one state (REM) appear in another (wakefulness). Narcolepsy is a relatively frequent disorder with a prevalence of 0.09%. A clear genetic component is indicated by the fact that over 90% of individuals with narcolepsy carry the HLA DR15 and HLA DQ6 gene, which is found in less than 30% of the general population. Siblings of individuals with narcolepsy have a 60-fold increased likelihood for developing the disease. Narcolepsy is thought to result also from abnormal neurotransmitter functioning and sensitivity and abnormal immune modulation. Clinical manifestations of normal sleep include (i) Excessive Daytime Somnolence (EDS); (ii) Cataplexy; (iii) Hypnogogic hallucinations; and (iv) Sleep paralysis. Whenever possible, the diagnosis of narcolepsy should be confirmed by polysomnography (PSG) followed by a multiple sleep latency test (MSLT).

Cataplexy:
Cataplexy, which occurs in 65% to 70% of the patients of narcolepsy, comprises of sudden loss of muscle tone, typically triggered by emotion such as laughter, anger, excitement, delight or surprise. The muscle weakness of cataplexy may be complete, resulting in the patients falling or being forced to sit; much more commonly, the weakness is milder and more focal, taking the form of facial sagging, slurred speech or localized weakness of an extremity. Cataplexy may never occur in 30% of patients with narcolepsy or may precede the onset of EDS. To reiterate, the salient features of Cataplexy are : (i) if severe and generalized, cataplexy may cause a fall ; (ii) more subtle forms exist with only partial loss of tone (eg., head nod and knee buckling); (iii) respiratory and extraocular movements are preserved; and (iv) cataplexy is usually triggered by emotions (especially laughter and anger)

Sleep Paralysis:
Sixty percent of individuals with narcolepsy experience sleep paralysis upon awakening from REM sleep (usually from a dream). This at-times frightening manifestation consists of total-body paralysis, with sparing of respiration and of eye movements, lasting from seconds to minutes.

The salient features of Sleep paralysis are: (i) usually the patient is unable to move upon awakening; (ii) less commonly, the patient is unable to move upon falling asleep with consciousness intact; (iii) paralysis is often accompanied by hallucinations; (iv) respiratory and extraocular muscles are spared; (v) paralysis occurs less frequently when the person sleeps in an uncomfortable position; and (vi) paralysis can be relieved by sensory stimuli (eg., touching or speaking to the person).

The following are also common features of narcolepsy : (i) a tendency to take short and refreshing naps during the day, these may be accompanied by dreams; (ii) trouble sleeping at night; (iii) nocturnal compulsive behaviours (sleep related eating disorder and nocturnal smoking); and (iv) obesity.

In children, the features of Narcolepsy are: (i) restlessness and motor over activity may predominate; (ii) academic deterioration, inattentiveness and emotional liability are common; (iii) at disease onset, children with narcolepsy and cataplexy may display a wide range of motor disturbances that do not meet the classic definition of cataplexy; (iv) motor disturbances may be negative (hypotonia) or active; and (v) motor disturbances may resolve later in the course of the disorder.

Diagnosis:
The DSM-5 defines narcolepsy as recurrent episodes of irrepressible need to sleep, lapsing or napping occurring within the same day. These must have been occurring at least three times *per week over the past 3* **months. There must also be presence of atleast one of the following : (i) episodes of cataplexy**

Cont...

occurring at least a few times per month; (ii) hypocretin deficiency; and (iii) REM sleep latency < 15 minutes or a mean sleep latency < 8 minutes and two or more sleep-onset REM periods (SPREMPs).

Narcolepsy can be categorized as mild, moderate or severe based on the frequency of cataplexy, need for naps, and disturbance of nocturnal sleep. In addition, the DSM-5 identifies five subtypes including (i) narcolepsy without catraplexy but with hypocretin deficiency; (ii) narcolepsy with cataplexy but without hypocretin deficiency; (iii) autosomal dominant cerebellar ataxia, deafness and narcolepsy; (iv) atuosomal dominant narcolepsy, obesity and type 2 diabetes; and (v) narcolepsy secondary to another medical condition.
Whenever possible, the diagnosis of narcolepsy should be confirmed by polysomnography (PSG) followed by a multiple sleep latency test (MSLT).

Pathophysiology:

Narcolepsy is thought to result from genetic predisposition, abnormal neurotransmitter functioning and sensitivity, and abnormal immune modulation. Current data indicate certain human leukocyte antigen (HLA) subtypes and abnormal hypocretin (orexin) neurotransmission, which leads to abnormalities in monoamine and actylcholine synaptic transmission, particularly in the pontine reticular activating system.

Management:

Treatment of Narcolepsy has both nonpharmacologic and pharmacologic components. Sleep hygiene is important. Pharmacologic treatment of narcolepsy involves the use of central nervous system stimulants such as methyphenidate, modafinil, dextroamphetamine sulphate, methamphetamine and amphetamine. These medications help reduce daytime sleepiness, improving the symptoms in 65% to 85% of patients.

SUGGESTEDD READING

1. American Academy of Sleep Medicine. International Classification of Sleep Disorders., 2 nd edition. Darien, IL: *American Academy of Sleep Medicine***: 2005.**

2. Plazzi G, Serra L, Ferri R (2008). Nocturnal aspects of narcolepsy with cataplexy. *Sleep Med Rev***.12: 109–128.**

3. Sehgal A, Mignot E (2011). Genetics of Sleep and sleep disorders. *Cell.* **146: 194 – 207.**

4. Lockrane B, Bhatia P, Gore R (2005). Successful treatment of narcolepsy and cataplexy. A review. *Can Respir J***.12: 225 – 227.**

5. Guilleminault C, Pelayo R (1998). Narcolepsy in prepubertal children. *Ann Neurol***. 43: 135 – 142.**

NAMS Regional Symposium on Sleep Medicine
Speaker : ***Dr.Ravinder Goswami***

SLEEP AND ENDOCRINOLOGY: HYPOTHALAMIC-PITUITARY-ADRENAL AXIS AND GROWTH HORMONE

SYNOPSIS

The suprachiasmatic nucleus (SCN) is the biological clock of the body determining the circadian rhythm. The neurons of the nucleus have inherent rhythm and set in biological day and night for humans. These periods usually correspond to day and night and indirectly to the cycle of sleep-wakefulness in most individuals. Retino-hypothalamic tract carrying photic stimuli from the retina provides the most important input to maintain the inherent rhythm of SCN. The rhythmic discharges from the SCN to various neurons of the central nervous system including pineal gland and hypothalamus translate into characteristic circadian rhythm for several hormones and metabolites such as glucose. As a result there is a pattern of hormonal changes occurring during cycle of sleep-wakefulness. Most characteristic of these changes are surge of melatonin with biological night, surge of GHRH at onset of sleep and surge of CRH during later part of the sleep. The cause and effect relationship of the hypothalamic releasing hormones and their target hormones on various phases of sleep including initial non-REM phase at onset of sleep and REM phase near awakening is an upcoming research area. Sleep EEG determining the onset of non-REM and REM sleep is an important tool complimenting the studies assessing relationship between various hormones and phases of sleep. The slow wave activity corresponds to the intensity of sleep at its onset during the biological night of an individual.

Besides, GHRH and CRH, several other peptide and steroid hormones including growth hormone, ghrelin, neuropeptide Y, estrogen and DHEAS are associated with, or have the potential to change phases of sleep including initial slow wave-non-REM sleep.

The sleep disturbances described with aging and depression are common. These are reflected as impaired slow wave activity in the EEG and early morning awakening. Recognition of sleep associated endocrine changes has resulted in a number of studies assessing sleep promoting effect of compounds such as melatonin and other compounds antagonizing CRH action at the receptor. These studies have potential therapeutic implications for patients with sleep disturbances associated with depression, aging and those having frequent night shifts.

The impact of misalignment between normal circadian rhythm of an individual and the sleep wake-cycle as observed during night shift has recently been recognized to result in important adverse consequences. These include difficulty in maintaining sleep during day time and cardio-metabolic derangement such as obesity, impaired insulin secretion and associated glucose intolerance. An understanding of Sleep-Endocrine physiology is clinically relevant for dealing with these adverse consequences.

SUGGESTED READING

1. **Morris CJ, Aeschbach D, Scheer FA (2012). Circadian system, sleep and endocrinology.** *Mol Cell Endocrinol* **349:91-104.**
2. **Steiger A (2003). Sleep and endocrinology.** *J Intern Med* **254:13-22.**

NAMSCON 2013