



CME Symposium on Sleep Medicine

6th December 2013



All India Institute of Medical Sciences
Jodhpur



Dr. S.N. Medical College
Jodhpur

National Academy of Medical Sciences (India)
and
All India Institute of Medical Sciences, Jodhpur
with
Dr. S.N. Medical College, Jodhpur

Handbook of Learning Resource Material

Venue :
Dr. S.N. Medical College
Jodhpur

Acknowledgment

Organizers gratefully acknowledge the contribution of following Residents and Medical Students of All India Institute of Medical Sciences, Jodhpur in decoding the Video and writing the script for this Handbook of Learning Resource Material

1. Dr. Vishesh Thanvi, JR Pediatrics
2. Dr. Rachna Pascal, JR Pediatrics
3. Dr. Mamta Shobhawat, JR Pediatrics
4. Dr. Baldev Sharma, SR Pediatrics
5. Abhijeet S. Bharath
6. Aviral
7. Rajat Ranka
8. Sulochana Saraswat
9. Revathy Menon
10. Aaditya Katyal
11. Priya Singhmour
12. Dhanesh Moten
13. Sakshi Khyalia
14. Amit Gupta
15. Sarthak Sharma
16. Tulsi Appat
17. Devansh
18. Prakrati Yadav
19. Vartika Kesarwani
20. Kkomal
21. Sonith Peter George
22. Rilshad A.K.
23. Ravi
24. Arun E J

**Scientific Programme: CME- Symposium on Sleep Medicine for UG students
6th December 2013**

Chairpersons

Dr Kuldeep Singh

Dr V K Vijayan

Dr. Suman Bhansali

S.No.	Time	Topic	Speakers
-	8.00-8.30	Registration	-
	8.30-9.00	Pre-symposium Assessment	
1	9.00-9.25	Physiology of Normal Sleep: From Young to Old	Dr. V. Mohan Kumar (DVD)
2	9.30-9.50	Pharmacology of Sleep	Dr. K.K. Sharma (DVD)
3	9.55- 10.10	Obstructive sleep apnea & Quality of Life	Dr Naveen Dutt (DVD)
	10.15-10.30	TEA	
4	10.30-10.45	Sleep disordered breathing: OSA, CSA, Pathophysiology and Diagnosis	Dr. V.K. Vijayan (DVD)
5	10.50- 11.10	Endocrine and Metabolic Aspects of OSA	Dr. R. Goswami (DVD)
6	11.15- 11.40	Co-morbidities associated with OSA	Dr. V.K. Vijayan (DVD)
7	11.45- 12.00	Childhood OSA	Dr. Rajeshwar Dayal (DVD)
8	12.00-12.25	Management of OSA	Dr. V.K. Vijayan (DVD)
	12.30-01.00	Live Interactive Session	Resource persons/ chairperson & participants
	01.00-01.30	LUNCH	
9	01.30-01.55	Stroke and Sleep	Dr. M.V. Padma Srivastava (DVD)
10	02.00-02.25	Sleep in Epilepsy	Dr. K. Radhakrishnan (DVD)
11	02.30-02.55	Causes of hypersomnia-Narcolepsy	Dr. M.V. Padma Srivastava (DVD)
	03.00-03.30	Live Interactive Session	Resource persons/ chairperson & participants
	03.30-03.45	TEA	
12	03.45- 04.10	Sleep and Endocrinology Hypothalamo-pituitary-adrenal axis (HPA) : Growth Hormone	Dr. R. Goswami (DVD)
	04.15-05.00	Problem solving Session	Dr V K Vijayan
	05.00-05.30	Post-symposium Assessment	
	05.30-05.45	Symposium Evaluation	
	05.45- 06.00	Valedictory Address	Dr Sanjeev Misra

CME Symposium on Sleep Medicine

Friday, 6th December 2013

Contributors

Prof. J.S. Bajaj

*Emeritus President, Chairman
Academic Council, NAMS, New Delhi*

Dr. V.K. Vijayan

*Advisor
Bhopal Memorial Hospital & Research Center (ICMR), Bhopal*

Dr. V. Mohan Kumar

Trivandrum

Dr. R. Goswami

AIIMS, New Delhi

Dr. M.V. Padma Srivastava

AIIMS, New Delhi

Dr. R. Dayal

Agra

Dr. K.K. Sharma

Noida

Dr. Naveen Dutt

AIIMS, Jodhpur

CONTENTS

CME Symposium on Sleep Medicine
Friday, 6th December 2013

S. No.	Topic	Author & Speaker	Page No.
1.	Physiology of Normal Sleep: From Young to Old	Dr. V. Mohan Kumar	4
2.	Pharmacology of Sleep	Dr. K.K. Sharma	8
3.	Obstructive Sleep Apnea and Quality of Life	Dr. Naveen Dutt	11
4.	Sleep disordered breathing: <i>OSA; CSA; pathophysiology and Diagnosis</i>	Dr. V.K. Vijayan	13
5.	Endocrine and Metabolic Aspects of OSA	Dr. R. Goswami	18
6.	Co-morbidities associated with OSA	Dr. V.K. Vijayan	23
7.	Childhood OSA	Dr. Rajeshwar Dayal	27
8.	Treatment of obstructive Sleep Apnea	Dr. V.K. Vijayan	31
9.	Stroke and Sleep	Dr. M.V. Padma Srivastava	36
10.	Sleep in Epilepsy	Dr. K. Radhakrishnan	42
11.	Causes of hypersomnia-Narcolepsy	Dr. M.V. Padma Srivastava	47
12.	Sleep and Endocrinology <i>Hypothalamo-pituitary-adrenal axis</i> <i>(HPA) : Growth Hormone</i>	Dr. R. Goswami	53

Physiology of Sleep : From Young to Old

Prof. V. Mohan Kumar

First of all I would like to thank Prof. Bajaj for kind words.

Good morning ladies and gentlemen.

Today I am going to speak on physiology of normal sleep from young to old. Whatever I am going to speak would be simple , very fundamental, probably known to many.....Many of you would know more than what I am presenting.

1. Physiology of normal sleep: From young to old

It is really difficult to find anyone who doesn't know about sleep. Also it is extremely difficult to find anyone who knows everything about sleep.

So with these few words I start.....

2. What is Sleep?

with what is behaviourally seen as sleep when you look at the behavioural criteria you find there is reduced motor activity, reduced activity per se , decreased response to stimulation and stereotype posture. To add to all this is the easy reversibility and this is particularly mentioned because it is unlike coma, hibernation, torpor and aestivation which are found in animals. Now coming to the scientific classification, scientific so called definition of sleep. It is defined on the basis of a few, primarily three electrophysiological signals namely EEG, EMG and EOG, representing the electrical activity of the brain, electrical activity of the muscles and activity of ocular muscles. In fact if you look at the definition and classification of sleep , one person's name stands apart, I mean it has to be remembered , Nathaniel Kleitman and who in as early as 1939 wrote a book about the kind of sleep and sleep classification. And later, Rechtschaffen and Kales gave the classification which is followed broadly even today. And very recently, if you can consider 2007 as very recent, the American Academy of Sleep Medicine gave some modification, essentially not much different from original classification as Rechtschaffen and Kales.

3. Sleep – wakefulness defined electrophysiologically

Now coming to the simple signals which are used for classifying and looking at sleep are EEG which as pleased can take from almost every part of the brain but you can have a parietal or occipital leads. And electrooculogram which gives the sense of eye ball movement and electromyogram pick up from the thin muscles.

4. Stages of sleep and wakefulness

Now I am really not going into the depth of classification because it will take a long long time and actually it is better done practically while record is taken. Just to give you an idea that the wake signals primarily have a desynchronised EEG and eye ball movements and EMG activity. And as you slowly go down to different stages, stage 1, 2, 3, 4 and the REM sleep, there is a difference primarily in terms of voltage and frequency of the EEG, changes in the EMG and ocular movements which suddenly changes during REM sleep about which I will spend a few few seconds.

5. Sleep-wake changes every night: Electrophysiologically assessed

Before doing that I would like to say that the changes in sleep wakefulness happens in a cyclic manner. In this very diagrammatically shown picture, you can see that person who goes from wakefulness slides down to stage 1, 2, 3 and stage 4 of sleep and spends a few minutes which is varying from 15 to 30 or even 40 minutes. And then suddenly he shifts back to a stage which is called the REM sleep. And this cycle continues with certain modifications throughout the night. So there is 5 to 6 cycles of REM, Non REM sleep usually occur in a healthy young adult.

6. NREM sleep

Now a few features, general, very general features of REM sleep I would like to go through. The human Non REM sleep which can be also called as slow wave sleep was traditionally classified into four stages and as I said a few seconds back American Academy of Sleep Medicine which actually governs and dictates what is happening in the field of sleep science, has classified stage 3 and 4 as one single stage for reasons which are difficult to explain within this short time. And what you see is, from NREM stage one to four, you will find a

successively deeper stages of sleep. And each of the deeper stages of Non REM sleep shows increasing voltage and decreasing frequency. And muscles including the upper airway muscles about which you will hear a lot today are progressively relaxed during deep Non REM sleep. And this muscle relaxation which was considered earlier was a passive relaxation, now we know that it is not just a passive relaxation, it is actually an active process which has in part the active hyperpolarisation of the lower motor neurons.

7. NREM sleep, continued

Now the body temperature is slightly reduced in Non REM sleep and this is also an active process. The body temperature is reset at a slightly lower level. It's not a passive lowering of body temperature because we are just lying without any activity. Heart rate and BP decline but there is an increase in the gastrointestinal motility. And there is generally a predominance of parasympathetic activity in all sleep stages and some of these changes in sympathetic, parasympathetic dominance would result in many of the consequences of disturbed sleep you will hear today and sleeper makes, I mean sleeper makes some postural adjustments throughout night roughly about 20 minutes or at intervals of 20 minutes and those awakened from Non REM sleep have poor sensory motor function. I mean, of course, anyone awakened from the sleep would have poor sensory motor function and this is poorer than what is compared from a person who is awakened from a REM sleep and Non REM sleep alternates with REM sleep and.....

8. REM sleep

The REM sleep, the name came itself because there are Rapid Eye Movements viz. REM and there are which are because of the bursts of movements of the eye ball. And correlated with REM, there are what is called the PGO waves Ponto-geniculo-occipital waves and which are difficult to be picked up in human beings but well picked up in animal experiments where you have the electrodes implanted deep into the brain and locally picked up and you can see the progression of the waves, starting from the pons to the geniculate to the occipital area. And EEG resembles that in animals to that in the wake state and that is why the term which is also used to describe REM sleep is paradoxical sleep, but usually used for describing the so called REM sleep in animals. In humans the EEG resembles that of the stage 1 of Non REM sleep viz. low voltage mixed waves. There is decreased thermoregulatory ability. Unlike what you saw in Non REM sleep, here there is a decrease in the thermoregulatory ability and the body temperature shifts towards the ambient temperature. On the other hand, the brain temperature and brain metabolism are increased during this phase. And there is a high parasympathetic tone with pupil becoming highly constricted but in between there are also sympathetic activities coming.

9. REM sleep, continued

Now, profound loss of muscle tone including the muscles of upper respiratory passage produced by hyperpolarisation. The first time it was demonstrated during the REM sleep or paradoxical sleep there is an active hyperpolarisation of lower motor neurons which is responsible for the muscle relaxation but later it was shown, it happens even during Non REM sleep. But the respiratory muscles, and those of the eyeballs, middle ear, they remain active, they are not actively inhibited. Muscles show sudden twitches in between also. There are also sudden respiratory changes, and increased heart rate and coronary flow. Respiratory responses to hypoxia is also blunted and not only hypoxia and responses to CO₂ is also grossly reduced. And there is a reduced waking threshold in humans; I mean I emphasize the fact because there is tremendously increased threshold in animals. There is a marked difference of what happens in animals and human beings.

10. Sleep pattern as the child grows

Now this change from sleep to wakefulness, as we all know, we have all experienced, the children; they have what is called polycyclic sleep pattern. In fact in most of the animals we see around also have polycyclic sleep pattern and a normal child, new born child passes through several cycles of sleep-wake, sleep-wake throughout day and night which is, of course is a nightmare for the mother and this slowly changes to a biphasic pattern by usually around the time that we in India send our children to the nursery or wherever we can send, but we always find that on these places where we send them, they insist that the child sleeps for a bit of time in the afternoon - because they actually have physiologically a biphasic sleep pattern with an afternoon nap, and which turns by the time they go to school, by-and-large into a monocyclic sleep pattern; can be reverted back during old age, mainly after age of 60, they shift back to a biphasic sleep pattern forcing them to have a slight nap in the afternoon.

11. Total Sleep Time

And as the child grows, there is a tremendous decrease in the amount of sleep, especially during the

initial stages - and initial ages, and this sleep by and large comes to a steady stage by the teenage, and then there is a slight decline. So in old age, there is a lower physiologically set certain amount of sleep. So when we see this pattern of elderly people complaining about not being able to sleep, it is physiological.

12. Human sleep pattern with age

And if you look at the different types of sleep, you find there is a decrease in the non-REM sleep and there is also a decrease in the slow wave sleep, and slow wave sleep, especially the deeper stages -stage 3, stage 4 and all- get tremendously decreased as we progress in age. Even as we pass 40-50 years, there is a tremendous decrease in these so-called deeper stages of sleep

13. Human sleep pattern with age

Which is normal physiologically. This is shown a little diagrammatically. So when the child is born, most of his sleep is REM sleep, and we know in few stages that the pattern of sleep or pattern of electrical activity picked up from the fetus primarily consists of a pattern which is resembling REM sleep . So that we can assume that the fetus is having by-and- large REM sleep and REM sleep, probably REM sleep alone. And as the child comes out, his NREM sleep is high and the premature child will have a higher amount of NREM sleep than other children, and it goes down, decrease within this log- scale below and we can see that there is a tremendous decrease in amount of sleep which is happening.

14. Theories of Sleep Regulation

Now few words about theories of sleep regulation.

Traditionally it was believed that prolonged activities during day time results in being tired at the end of the day and it is followed by rest, at night, in form of sleep. Even great people like Charles Sherrington and Pavlov used to think that it is a passive state which is happening. Now sleep, around 1950's, the whole concept changed, and the passive state theory was replaced by an active state theory. And it was considered active because we know that the brain activity only marginally gets reduced during sleep. So they are employing various modern techniques and then they found out that if it is an active state, there must be some regions of brain which are responsible for that.

15. Simplified Diagram of Sleep - Wakefulness Modulating Circuit

Of course this is my field of study and I am really not going to spend much time on it, except showing a very simplified diagram to show that there are certain regions of the brain which are primarily identified, with the thalamus and the cortex as the center streak in the whole regulatory process, primarily changing the EEG. And this thalamus and cortex is influenced by other areas in the brain, especially the brain stem, posterior hypothalamus and the basal forebrain and the caudal brainstem. They interact with thalamus and also interact with the cortex, and the basal forebrain and caudal brainstem primarily have been ascribed the role of producing so-called NREM sleep, and the brainstem and especially posterior hypothalamus have been ascribed the role of producing wakefulness; and the brainstem, especially in around pons, have the additional circuit responsible for the REM sleep.

16. Sleep is Auto - Regulatory Global Phenomenon

Now we have passed several of these theories and we know now that to say that some circuit like this is responsible for sleep is rather over-simplification, because we know that sleep is not a state and the cyclic pattern of change in the activity is found throughout the brain. Every part of the brain has role, and now we can say that- without going into much detail- sleep is neither an active nor a passive state. All brain segments have inherent sleep-wake oscillation. Dynamic interaction of neuronal network throughout the brain ultimately results in this shift from wakefulness to sleep. And different sleep signs occur, and the division of sleep into non-REM and REM is also within certain limits. We look at certain signs that we are looking at, and we are seeing, we are observing, on the basis of which we say this is non-REM and this is REM; and sleep signs add only the state specific qualities to sleep and wakefulness. Basal forebrain and hypothalamus actually have a role in integrating sleep with many of the vegetative functions.

17. Sleep-Wake cycle with and without External Clues

And also I should say a few words that we have a 24 hour sleep-wakeful pattern - we all follow that , and this sleep-wakeful pattern of 24 hours is not really the one which set by the brain. There are some regions in the brain which are primarily responsible for setting this cycle, and that sets the cycle to about 25 hours, thus more than our normal 24 hours rhythm. This can be shown if you put a person in an environment which gives the

external clues, he follows the 24-hour pattern. But if you put him in a situation like in a cave or in an isolated room where there is no clue of the external world, then you find that slowly his sleep is shifting every day by an hour or so, and in such a way that once he is taken back to the environment, his cycle returns back to normal 24 hours cycle. So there is an environmental influence which also influences our sleep-wakeful pattern.

18. Is Sleep essential for life?

Sleep deprived animals- I know it's inhuman but we cannot show it in human beings-if you deprive an animal of sleep, it dies in 2-3 weeks, but it is startlingly different if you deprive a rat of food, it takes up to 4 weeks, and it can live up to 4 weeks. So sleep is something more important than food. Now sleep is preserved throughout the evolution, and this may not be apparent in form of sleep and wakefulness, defined as per the criteria given for human beings - they sometimes have a rest activity cycle. All mammals have so-called REM-NREM cyclic alternation. And any part of the sleep which is deprived has a rebound - if you deprive a person of REM sleep, there is a rebound, and man shows very disturbed behavior after sleep deprivation about which you are going to hear a lot and lot.

19. Functions of Sleep

A few words about what are functions of sleep. It is said that sleep facilitates the synthesis of molecules that protect the brain cells from oxidative stress. And it is also said to be restorative. What is restorative? Sleep may be having a restorative and recovery function, especially for the brain. There is certainly an energy conservation, a slight reduction in whole metabolism by about 15%, and it also has something called a thermoregulatory function. Many neurons which are ascribed as playing a role in sleep regulation are also altering its firing, altering its activity with change in temperature, external or internal.

20. Functions of Sleep

And brain growth. We also find that some part of sleep, especially REM sleep has a role to play in terms of brain growth - probably that's why fetus has a lot of REM sleep, and a newborn who not has a fully developed brain in that sense that we find in some other animal, where you find a lot of REM sleep, and in fact if you look at those animals which are almost self-sufficient when they are born, they have much less amount of REM sleep. Now it also facilitates neurogenesis. We used to think that in brain, cell development and multiplication is coming to an end by the time we are born, now we know it's not true, and there are certain regions, especially in the dentate gyrus and all, where cell proliferation still continues and this is affected by sleep deprivation. And there is what is called memory consolidation. In fact if you look at the literature during the last 10 years, probably 15-20 times increase in the number of papers, which are coming to substantiate memory consolidation or theory of sleep; that does not mean that we know the last word about it, it still is a debatable factor. Discharge of emotions through sleep is something which has been ascribed function, and we daily experience it.

21. Sleep is essential for life

I will like to conclude by saying that there are many physiological changes, essential for life, occur during sleep. I want to emphasize that we know some functions of sleep, there are many we still do not know, many we still do not know. Electrophysiologically and behaviorally defined sleep do not explain all the aspects of sleep. Importance of sleep for health and survival is best demonstrated by disastrous consequences resulting from sleep deprivation.

Thank You

Pharmacology of Sleep

Dr. K. K. Sharma

Sleep is a global process regulated by brain utilizing multiple neuro-chemical systems. Neurotransmitter for the systems, they function independent of each other as well as integrating with each other. If we cause loss of one system, it would not allow the other system to work less rather than will try to compensate. Most of these ARAS neurons produce low voltage, fast frequency activity, as told by Dr. Mohan Kumar in the EEG and increased muscle tone in EMG and diffusely activate the cortex and other forebrain regions.

NREM sleep is mainly driven by neurons in the pre-optic area and various neurotransmitters which subserve these functions is GABA and to some extent other neuropeptides like Encaphalins and Galanin. All three are inhibitory neuropeptides.

REM sleep is regulated primarily by neurons in pons with additional influence arising from the lateral hypothalamus by using neurotransmitters Acetylcholine, Monoamines, GABA, melanin concentrating hormone, which interact with the glutamate and GABA neurons of the sub-laterodorsal nucleus which is also known as the Subcoeruleus nucleus because it is situated just below the locus coeruleus which project to the ventromedial medulla and ventral horn of the spinal cord, providing pathways through which they may inhibit the motor neurons and decrease the atonia or produce the atonia and decrease muscle tone during the REM sleep.

Activation of the SLD region elicits atonia and REM sleep like EEG activity, it is also known as the paradoxical sleep because it has got the characteristics of EEG that is low voltage, fast activity amplitudes, that's why its EEG activity is similar to the wakeful state.

Then there are certain mutual inhibitors of these wake and sleep regulating regions that help to generate the full wakefulness and sleep with rapid transitions between two sleeps NREM and REM. Besides that, some homeostatic sleep factors like, which we call Somnogens, are also produced in the brain by the over activity and more energy requirements and specially at the time where there is long wakefulness and these substances are known as Neurosin Cytokines like IL-1B, TNF, PGD2 and NO. All they are known as Somnogens because they produce sleep or facilitate sleep after long wakefulness. So there are drugs which can target them during the situation where there is sleeplessness. So a broad understanding of these transmitters, mechanisms in Wake-Sleep cycle allow clinicians and researchers to better understand the drugs, lesions and neurological disease of sleep and wakefulness and consequently their use to rationalize the pharmacotherapy of the sleep disorders.

Clinical Pharmacology of sleep medicine can be loosely classified into drugs aimed at treating-

1. Sleepiness that is hypersomnia and that is-
 - Excessive day time sleepiness – Narcolepsy, Cataplexy
 - Shift work disorders - jet lag -
2. Sleeplessness, that is insomnia
3. Sleep related movement disorders—and there is
4. OSA - the main theme of this program. Although most of the drugs are available by prescription only, the stimulants caffeine and the antihistamine : Diphenhydramine are common over the counter options for each and everyone for using in sleepiness or sleeplessness respectively.

So we go for the excessive sleepiness treatment which is important at the time when there is increased sleepiness.

The primary hypersomnias are uncommon compared to disorders which include sleepiness as a secondary symptom to sleep disruption.

When the patient reports sleepiness, it is important to investigate potential causes such as sleep apnea or insomnia. Pain syndromes, mood disorders and general medical problems may be comorbid with sleep apnea and or disrupted sleep.

However, residual day time symptoms persist in some patients despite of optimized management of the potential primary causes leading to considerations of stimulant agents in the appropriate clinical situations.

Narcolepsy and Cataplexy

Narcolepsy is a rare disabling disorder affecting about 25 over 1 lac persons and characterized by excessive day time sleepiness, abnormal rapid eye movement, sleep manifestation including Cataplexy that is sudden loss of muscle tone triggered by the strong emotions.

Direct transitions from wakefulness to REM sleep that is, DREMs.

Sleep paralysis inability to move limb following awakening from the REM sleep and hypnagogic hallucinations.

Hypnagogic hallucinations occur around sleep onset or awakening or sleep paralysis.

Narcolepsy is caused by deficient neurotransmission by orexins because orexins are the neuropeptides which are involved in controlling all neurotransmitters which are excitatory and responsible for wakefulness.

They are released by the neurons of the lateral hypothalamus with widespread projections namely to aminergic neurons Histamine, Dopamine, Norepinephrine, 5HT and known to be involved in control of

wakefulness for eg Histaminergic, dopaminergic, noradrenergic and adrenergic.

Histaminic neurons seem even to be necessary for the waking action of orexins and reduced level of histamine in CSF have been reported in narcoleptic patients recently.

The drugs which are used in the treatment of hypersomnia can be divided into different groups

1. is stimulant-acting on the noradrenergic - dopaminergic system.

This group of drugs is known as amphetamines this is Methamphetamine, Dextroamphetamine. They are used for excessive sleepiness such as Narcolepsy or phase shift disorders. Methylphenidate, Dexmethylphenidate then Modafinil, Armodafinil -all these three act via increased release of the Dopamine as well as Norepinephrine in the brain.

Besides Modafinil which only acts on Dopamine and Norepinephrine, Amphetamine produces derangement neurons of both dopaminergic and norepinephrine and thereby they cause continuous release and leading to reinforcement of the behavioral addiction or habituation is very common, with amphetamines rather than Modafinil or Methylphenidate. These drugs are used in Narcolepsy, Modafinil is preferred because it decreases daytime sleepiness and used for shift work disorders it increases the latency during nighttime shifts. Modafinil/Armodafinil showed less need for recovery sleep after sleep deprivation and fewer sleep disturbances with no REM sleep deficit.

Caffeine we know is present in various Cola drinks, soda drinks, health drinks and also acts as a stimulant and today we know the mechanism is by antagonism of adenosine. Adenosine we have just seen one of the Somnogens which act by inhibition of Histaminergic and Monoaminergic pathways. So Caffeine by inhibiting the activity of Adenosine, increases the wakefulness producing monoamines like histamine, nor-adrenaline and dopamine.

Sometimes we use antidepressants. Antidepressants, although we know they produce depression and sedation but they are used to promote the increased noradrenergic tone specially amitriptyline, protriptyline with or without gamma-OH-butyrate, that is sodium oxybutate, which is used to improve nighttime sleeps in narcoleptics because they have got day sleepiness.

Now other newer therapies which include Pharmacological agonists of the Orexins

Orexin is a neuropeptide which is stimulatory so orexins have got two receptors OR-1 and OR-2. Now there are some receptors, some drugs which act on the orexin receptors which are in the pipeline of the clinical evaluation and I have not named them because they all are coded compounds but there is a drug which is known as Almorexant which is not an agonist and rather antagonist and another compound MK-4305 which is a Suvorexant compound which is in the development for the treatment of the hypersomnias. Then other options are transplantation of the orexin neurons, Orexin G-therapy because these are the ones which are destroyed during the Narcolepsy Cataplexy syndromes.

Histamine H receptors antagonists or inverse agonist like Ciproxifan, Tiprolisant, Pitolisant are under development and they have gone under phase-3 clinical trials and have been recommended for the treatment of excessive daytime sleepiness observed with Narcolepsy. The awake promoting affect is likely to be mediated by increased histaminergic response to the H3 receptor agonist absent in animals which have gone loss of the H1 receptors.

Now we come to insomnia -excessive sleeplessness.

Insomnia is defined as the insufficiency in quality or quantity of sleep and is most prevalent sleep disorder.

Approximately 50% of the adults complain occasional insomnia and 10-15% chronic insomnia. Insomnia can involve difficulty falling sleep, staying sleep or poor quality of sleep. Insomnia can be considered a constellation of symptoms with variety of underlying causes. As a symptom it can be secondary to disorders of mood, pain or variety of other neurological and general disorders.

Insomnia is classified into two groups Co-morbid with other underlying causes or primary where the secondary causes are not there. Consequences of insomnia include day time sleepiness, lack of energy and cognitive impairment. Insomnia may even precipitate or accompany the development of psychiatric symptoms.

One of the most intriguing and yet poor understood aspect of the insomnia is the misperception phenotype persons in which person underestimates their sleep time compared to objective measurements.

Insomnia can also be presented as a feature of Circadian phase disorders most commonly delayed Circadian phase and especially seen in jet lag.

The primary challenge with regards of treatment of insomnia is that both entirely depend on the clinical history with no basis of objective testing.

Pharmacological agents which are used in the treatment of Insomnia fall into various groups and all of them are known as sedative hypnotics.

First group is Benzodiazepine and other is Non-Benzodiazepine. That is they have got activity similar to benzodiazepines but structure is not benzodiazepine

They are known as "Z" drugs, Zaleplon, Zopiclone, Eszopiclone, Zolpidem.

BZD group of drugs everybody is acquainted with them, Alprazolam, Nitrazepam Diazepam , Flunazepam . etc.

Another group is Antihistamines H1 blocking agents-

Diphenhydramine, Pheniramine and Chlorpheniramine.

Then there are drugs known as Melatonin or Melatonin derivatives, Remelteon is an agent which has been shown to be MT₁, MT₂ agonist like Melatonin and 6-16 times more potent than Melatonin and is used in driver sleep disorder and jet lag sleep disorders.

The another group is 5HT antagonist-

Ritanserin which is antagonist of 5HT_{2a} and 5HT_{2c} receptors because 5HT is one of the important wakefulness producing amines in the brain.

Then we have got the antidepressants such as Tricyclic depressants Amitryptaline, Nortryptaline and you will be surprised that they are used in both hypersomnias and insomnias because their activity depends on when there is insomnia they produce sleep and when there is hypersomnia there is a increased day time sleepiness so they antagonist. So selective serotonin reuptake inhibitors like Fluoscetine, citraprolam, trozactone which is a special agent has got not only activity of inhibiting reuptake but also antagonizing 5HT_{1A}, 5HT_{2A} and alpha₁ receptors.

Then there is a new drug Agomelatine, which is a Melatonin derivative which has got the unique property of having melatonin receptor agonizing activity and serotonergic 5HT_{2C} receptor antagonist and this is a very good agent for the treatment of the jet lag sleep and diurnal disturbances in the sleep. A variety of other compounds used to treat insomnia antagonize histaminergic orixanergic wake promoting nuclei and compound is almorexant have been shown to enhance REM and NREM sleep and reduce wakefulness, in animals, healthy humans and insomnia patients.

Now there are some situations which we discuss specially under these topic one is the-

1. Sleep related movement disorders.
2. Restless Leg syndrome
3. Periodic limb movement activities in the sleep are the most common sleep disorders resulting in sleep disturbances.

The former is strictly clinical diagnosis while the latter is a polysomnographic finding PLM may also be seen in Narcolepsy, sleep apnea and REM behavior disorder. Both are treated similarly often beginning with the investigations for iron stores, Sr. ferritin and oral repletion with iron because it has been shown that Fe is a very important cofactor for the rate limiting step for tyrosine hydroxylase for the synthesis of Dopamine. SO if there is Fe deficiency Dopamine is reduced because of that Fe repletion is very important so that dopaminergic system can work properly.

Then other drugs which are used for this purpose are Dopaminergic Agonist

Ropinerole which are off label use of other classes of agent. Then REM behavior disorder is most commonly treated with hypnotic BZDs that is clonazipine which is first choice or melatonine given prior to the bedtime.

Then I would like to stress on the RBD – sleep behavior disturbance, because it is more common in people with 50yrs age and it is shown that RBD has been shown to precede and predict the later development of the neurodegenerative disease known as synucleinopathies including Dementia, Parkinson Disease with Lewis body and Multiple System Atrophy.

It suggests that neurodegenerative process in the generation of idiopathic RBD presumably occurring in the brainstem, REM muscles atonia generation zones and the dorsolateral Pons and medulla.

RBD may be an important biomarker allowing early state preventive treatment for synucleinopathies since RBD often occurs many years earlier than the other conditions.

The acute form of the RBD is managed by withdrawal of offending medication that is antidepressants where as chronic form is treated symptomatically by BZD clonazepam which is first drug of choice followed by melatonine prior to bedtime. This is very important to treat the RBD condition because it is a predisposing factor for various degenerative diseases including the Parkinson at the later stage.

Now the treatment of the obstructive sleep apnea will be dealt in detail by other learned speakers but the only thing I would like to stress is the drugs which are used for this purpose. Pharmacological interventions to treat OSA increase the activity of the upper airway dilator muscles as well as the ventilator drive for eg. Noradrenergic drug, protryptaline serotonergic agents like Fluoxetine, progestagen and bronchodilators like salbutamol.

Besides the standard treatment using the CPAP that is the continuous positive Airway Pressure. So these drug acts as an adjuvant with the therapeutics which will be dealt by the speakers later on.

Then post-traumatic stress disorder which is related to the nightmares and for this purpose we use BZDs, selective serotonin reuptake inhibitors, that is atypical antidepressants like Nephazdone, Triozedone, Beta-blockers and alpha adrenergic antagonist Prazosin. Prazosine is very important for this purpose because it reduces the incidence of the nightmares and bad dreams in the situation.

Thank You very much.

Quality of life in patients of OSA

Dr. Naveen Dutt

Respected Professor Bajaj, Professor Mohan, fellow speakers and my dear friends.

Today's topic of my presentation is "Quality of life in patients of obstructive sleep apnoea."

First of all the definition of 'quality of life' – WHO defines quality of life as individual's perception of the present position of life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards in concern.

Two things are important here –

1. Individual perception. There is no test, no objective test to measure quality of life and
2. It is measured in relation to the goals, expectations and standards of the person. Two people, they might be having equal assets, same kind of relationship, same physical health, but they might have different quality of life because their perceptions, their expectations from life are different.

Quality of life is a broad concept. There are multiple factors which affect it like – physical health, psychological state, level of independence, social relationships. Physical health is just one of them. Now what is the difference between quality of life and health related quality of life. See, the health is one of the parameters which affect quality of life. The all determinants of quality of life are not health related, like poverty. Poverty is not going to affect health. So only the domain which is affected by health is included in health related quality of life.

Then why do we need to measure health related quality of life? See, for this we have to go back to 1980's because the concept of quality of life is of 80's. In that era there was shift of focus towards chronic disease. Cancer posed a unique challenge, and there was stress on patient point of view.

In western world in 70's and 80's there was shift of health care resources from acute infectious disorders to chronic disease prevention and treatment of chronic disease is associated with long term treatment with its own side effects, so there was need to study overall impact of disease and treatment on life, not just the effect of disease and it was noted that emotional suffering from cancer is as good as the disease itself, the physical suffering part. So it was soon realised that at times treatment of cancer is as troubling as disease itself so just prolongation of life by few months is not sufficient but quality of life of the patient must improve.

The patient's point of view. The patient doesn't come to the doctor for normalisation of biochemical parameters, he wants improvement in quality of life.

Then why do we need to measure quality of life in OSA- Apnoea hypopnea index, which is index of severity in OSA. It fails to adequately measure broader impact of disorder on human life, because it doesn't take into account the sleep fragmentation and other things which happen in OSA, and being tied to a machine 8-10 hours a day out of total 24 hours is also something unique and has its own problems. Surgery and other therapeutics modalities are also associated with significant consequences important for the patient.

And it helps in early detection of comorbid illness.

Burden of OSA in India.

The awareness is low, number of cases is less, but still prevalence is sufficiently high. I came across only 4 studies of prevalence and the prevalence was 3.5% - 15.5% in those studies.

Quality of life is, how do we measure quality of life in OSA, quality of life is subjective perception measured with the help of questionnaires. These questionnaires have separate domains like physical health, mental health and social health domains. These are present in almost all the questionnaires, and the answers are usually in the form of Likert scale. It is a form of graded response and this response are numbered, like if patient is having very large problem, the questionnaire is of the format – how much problem have you had from not being involved in family activities- a very large problem, large, moderate to large, moderate, small to moderate, then each is given some number according to the response. All scores are counted to get the domain score and total quality of life score.

There are two types of questionnaires.

One is generic questionnaire and other is OSA specific questionnaire. The generic questionnaire can be used in any disease or condition to measure quality of life, but OSA specific questionnaires are those which can be used in OSA only.

Which ones are better, it depends on the research question. If you are going to compare between the two things, two different indices, then only generic questionnaires can be used, but the research studies, they are more inclined towards disease specific questionnaires.

Quality of life in OSA patient.

The first study of quality of life in OSA was performed in 1993. The study observed that there was significant quality of life impairment in OSA patient, and interestingly, in some severe OSA patients there was little quality of life impairment. In late 90's and early 2000, there were multiple studies exploring the relationships of quality of life and OSA. These early studies used generic questionnaires to measure the quality of life, not the

disease specific ones. And most studies they found there was significant impairment of quality of life in OSA patients. In 1998 Flemons and Riemer they developed Calgary sleep apnoea index which is an OSA specific questionnaire. After this index the trend was use of disease specific questionnaire in OSA quality of life studies.

And now, what is the association of quality of life with OSA severity, most studies they have not found association of quality of life impairment with OSA severity .there is no clear evidence that severe OSA patients have most severe impairment of quality of life as compared to mild and moderate patients. This study was conducted by us in Government Medical college Chandigarh in which we found that all the domains of Calgary scale showed significant impairment in quality of life in OSA patients, and impairment was not proportional to severity of disease.

What is the effect of CPAP on quality of life.

CPAP is the standard treatment for OSA, but how is it divided on this question. Cochrane review in 2006 observed that CPAP improves quality of life measured in OSA patients, but it took into account many primary and secondary endpoints. A meta-analysis in 2008 which studied quality of life only, it concluded that CPAP did not improve general quality of life but did improve scores in some domains. Even if quality of life improves in patients but not all patients it improves. In a substantial proportion of patients neurobehavioral responses will not normalise despite seemingly adequate CPAP use.it is thus crucial to adequately assess patients after CPAP therapy and seek alternate aetiologies and treatments for any residual abnormalities.

This is very interesting study.it was presented in ATS in 2011.it was a large multicentric study. They took patients who were diagnosed with OSA but apnoea hypopnea index between 5 to 15.they were not recommended CPAP on the basis of symptoms.so the patients were randomised into two halves. Half patients were given 6 months CPAP trial and other patients were not given any treatment and the quality of life scores was also significantly higher in CPAP group compared to the standard care patients, and the authors they wrote – "it appears clinical assessment of patient with OSA does not reliably identify all patients likely to benefit from CPAP.in other words, authors suggested impairment of quality of life maybe an indication for starting treatment.

The take home message from this presentation is – it is important to measure Quality of life in your OSA patients. Patient doesn't expect us to decrease their apnoea hypopnea index, but they expect us to improve their Quality of life. Apnoea hypopnea index with CPAP is not adequate, post CPAP quality of life should be measured.in many patients neurobehavioral conditions and Quality of life do not improve after CPAP. Alternate aetiologies must be looked for in such patients, and recent research suggests that impaired Quality of life maybe indication for starting treatment in OSA patients.

Thank you.

Sleep disordered breathing: OSA, CSA, Pathophysiology and Diagnosis

Dr V K Vijayan

Professor Bajaj, Prof Mohan Kumar, respected speakers, delegates and my friends. These are the subsets of sleep disordered breathing. They are intermittent snoring, obstructive sleep apnea, can be obstructive sleep hypopnea (OSHA), obstructive sleep apnea syndrome, upper airway resistance syndrome, central sleep apnea, mixed apnea and overlap syndrome

Next slide: (sleep apnea)

Obstructive sleep apnea is repetitive interruption of ventilation during sleep caused by collapse of the pharyngeal airway whereas central sleep apnea is repetitive cessation of ventilation during sleep resulting from loss of ventilator drive. Both are interruption of ventilation whereas in OSA there is collapse of pharyngeal airway, in CSA there is loss of ventilator drive. Mixed apnea is that both be present but starts with central apnea and ends with obstructive sleep apnea.

Next slide (Central Sleep Apnea)

These are the manifestations of Central sleep apnea one is high altitude- induced periodic breathing, idiopathic CSA, narcotic induced central apnea, obesity- hypoventilation syndrome and Cheyne- stokes breathing.

Next slide (pictures)

See in normal individuals during sleep the airway is patent during inspiration and expiration air can flow freely. But during OSA you can see here tongue is falling back and obstructing the upper airway therefore there is obstruction during ventilation and this is one of the important mechanical factor for obstruction to breathing.

Next slide (Obstructive sleep apnea)

When will you say there is obstructive sleep apnea? OSA is cessation or near complete cessation that is more than 90 % reduction of airflow for more than or equal to 10 seconds despite continuing ventilatory effort- there should be continuing ventilation. There should be 5 or more such episodes per hour of sleep. Usually it is associated with a decrease in more than 4 percent in oxy-hemoglobin saturation.

Next slide

You can see it is depicted here. There is cessation of breathing airflow limitation, during this you will be recording of abdominal and thoracic movements... Normal individual movement will be in same direction whereas in Obstructive sleep apnea you can see there are paradoxical movements, this is followed by when arousal takes place when arousal takes place there is deep inspiration which is followed by desaturation this is obstructive sleep apnea

Next slide

Hypopnea is there is reduction in airflow more than 50 percent compared to baseline. This will be followed by and arousal from sleep and this is associated with a decrease in oxy-hemoglobin more than 3 percent and the event lasts 10 seconds or longer

Next slide

There you can see obstructive sleep apnea there is complete cessation here there not complete cessation but reduction in more than 50 percent associated with paradoxical movements associated with desaturation

Next slide

The other terminology is upper airway resistance. In this case there is no significant decrease in airflow but there will be snoring. Fifteen or more episodes of arousal per hour of sleep will be present. No significant decrease in oxyhemoglobin saturation.

Next slide (Graph)

There is no cessation, no de-saturation when arousal is present

Next slide: Reporting..)

Now what is apnea- hypopnea index- This is the number of apneas and or hypopneas per hour of sleep confirmed by electro-encephalogram. The other index is Respiratory disturbance index. In this case number of apneas, hypopneas and respiratory effort related arousals per hour of sleep, again, confirmed by EEG

Next slide

This is the classification of severity of OSA when AHI is more than 5 but less than 15, it is mild, more than 15 and less than 30 is moderate and more than 30 is considered severe OSA. The other terminology is Obstructive sleep apnea syndrome- see when OSA is associated with excessive day time sleepiness it is classified as Obstructive sleep apnea syndrome.

Next slide:

The other terminology is Pickwickian syndrome- Obesity hypoventilation syndrome. In this consists of obesity, sleep disordered breathing, hypoxia and chronic hypercapnia during wakefulness in the absence of other known causes of hypercapnia. This was described as “Pickwickian syndrome” in a case report in 1956 and this patient had resembled a character depicted by Dickens in his story, “The posthumous papers of the Pickwick club”, because both were obese with excessive hypersomnolence.

Next slide:

What is this overlap syndrome? This is defined as the occurrence of both chronic obstructive pulmonary disease and sleep apnea-hypopnea syndrome in an individual. Both are common, both are diseases affecting adult population mostly over 40 years of age.

Next slide: (table)

What is the prevalence rates of OSA in our country and globally. This is the prevalence of of OSAS in different studies. It is 2 percent in females and 4 percent in males

Next slide (table- Indian)

What is the situation in our country? See there are only few studies. The first one is from Mumbai by Udwadia- this is not a community based study. This is a hospital based study where male insurance claimers had 7.5 % of OSAS. This is our study and these are from All India Institute. In our study in randomized control study OSA was 1 percent in females and 2.4 % males. This study from All India Institute by Sharma had 2 percent females and nearly 5 percent males.

Next slide

What are the patho-physiological changes.

Next slide

There are some risk factors that are non-modifiable and others are modifiable. Non- modifiable factors are age- you cannot modify age- as age increases. Male gender – more common in males, ethnicity, anatomical abnormalities of craniofacial region- there is narrowing of upper airways. Neck circumference more than 17 inches in males and more than 16 inches in females. Genetic predisposition, if there is a family history of sleep apnea.

Next slide:

These are Modifiable factors- one is obesity, use of alcohol, sedatives or tranquilizers, a narrow airway- enlarged tonsils or adenoids especially in children, smoking, chronic nasal congestion, hypertension, diabetes mellitus and menopause.

Next slide (figure)

See, you can see here – this is normal individual, normal bony structure, normal fat and this will be the size of upper airways. When there is obesity, the person will have fat in upper airways and even though the size of airway may be normal, because of excessive fat, there will be narrowing of upper airways causing obstruction. If there is bony cage abnormality, the size of airway is small compare to normal, even the fat deposition is normal, there will be reduction in airway causing the obstruction to the upper airway.

Next slide (Figure)

Again, one of the important muscles, that keeps upper airways open is genioglossus muscle. When there is inspiratory mechanical receptor present in upper airways through superior laryngeal nerve, NTS, hypoglossal motor nucleus stimulates this one. When there is obstruction, this also control one, the brain input will be less there will be not much to the genioglossus muscle.

Next slide (figure of saggital section of Pharynx)

This is important factor which keeps from collapse and keeps airways open. See, when there is deposition of fat it will be collapsing. When there is the pharyngeal muscle will be contracting and lung volume increases there will be opening of airways.

Next slide:

These are the OSA induced Biological changes. One is intermittent hypoxia. When there is repeated episodes of hypoxia, lasting 10 second to 2 minutes, and normoxia, resembles ischemia reperfusion events. That means, there will be episodes of hypoxia normoxia. This hypoxic ischemic phase the cells adapt to low oxygen environment. Reoxygentaion reperfusion phase there is sudden increase of oxygen in the cells resulting in production of reactive Oxygen species. Others are intermittent hypercapnea and sleep fragmentation.

Next slide

These are the pathophiological changes in OSA- Intrathoracic pressure changes, sympathetic activation, oxidative stress, systemic inflammation, metabolic dysregulation, endothelial dysfunction, hypercoagulation, and neurohumoral changes.

Next slide:

Intrathoracic pressure changes- there is repetitive inspiratory efforts against a closed upper airway – this leads to increased negative intrathoracic pressure. An increase in transmural gradients across the atria, ventricles and aorta. Many complications of cardio-pulmonary is due to this. This is similar to Muller maneuver in which inspiration against closed glottis leads to a pleural pressure of – 30 cm of water. This leads to autonomic and hemodynamic instability in OSA.

Next slide:

Now next one is sympathetic nerve activation. There is increase sympathetic activity during sleep due to activation of peripheral chemo-receptors due to hypoxia, hypercapnea, apnea. This results in peripheral vasoconstriction and increase in Blood Pressure. And there is also increased concentrations of catecholamines in urine, an increase in resting heart rate during wakefulness suggest that there is chronic sympathetic nerve activation in OSA.

Next slide:

Another important is oxidative stress. Thiobarbituric acid reactive substance formation is higher in patients with OSA compared to healthy subjects. CPAP treatment, that is most important for treatment of OSA, decreased the nocturnal levels of TBARS and peroxides in patients. Inhibition of xanthine oxidase by allopurinol and use of supplemental Vitamin C, that is an anti-oxidant, improved endothelial function in OSA patients. There is importance of increase in 8 Hydroxy 2 deoxyguanosine excretions in patients with severe OSA suggesting oxidative DNA damage. This also increased oxidized low density lipoprotein levels in OSA. These suggest that OSA is associated with increased oxidative stress.

Next slide: (bar diagram)

We have also observed oxidative stress in OSA. This is control, this is OSA subjects, this is after CPAP and this after anti-oxidant. You can see that there is significant increase in Oxidative stress which after CPAP

treatment and after anti-oxidant significantly came down.

Next slide:

We also looked into new reduced glutathione levels which were higher in control and were increased with CPAP and anti-oxidants.

Next slide:

Now come to systemic inflammation. CD4 and CD8 T Cells of patients with OSA undergo phenotypic and functional changes, with a shift towards type 2 cytokine dominance and increased IL- 4 expression. IL 10 negatively and Tumor Necrosis Factor alpha Positively correlated with severity of OSA. There is an increased level of C Reactive protein in OSA. There is increased in NF Kappa B, an important factor for activation of inflammatory pathways. There is also increased expression of adhesion molecules and increased adhesion of monocytes to human endothelial cells.

Next slide:

Nitric Oxide is an important substance which keeps endothelial dilatation and there is reduced Nitric oxide in exhaled alveolar in OSA. Endothelial dysfunction as evidenced by altered Nitric oxide dependent vasodilatation, reduced NO release from endothelium because of oxidative stress, interaction between NO and free radicals lead to formation of peroxynitrite promoting a variety of biological cascades leading to atherosclerosis.

Next slide:

There is procoagulant activity as evidenced by elevated levels of plasma fibrinogen, exaggerated platelet activity, reduced fibrinolytic activity, exaggerated platelet activity is reduced with CPAP treatment. There is hypercoagulable state in OSA.

Next slide: (Figure)

See what is happening in OSA- see you can see there is apnea, and when there is apnea followed by arousal, there is desaturation, reduced level of oxygen stimulates carotid bodies. This lead to sympathetic activity to the brain and also there is tachycardia nervous system stimulation and because of changes in intrathoracic pressure there is negative feedback to the brain.

Next slide (Figure)

This is the proposed mechanism of OSA and cardiovascular diseases. There will be intermittent hypoxia and this leads to sympathetic excitation, systemic inflammation, oxidative stress and metabolic dysregulation. All these leads to endothelial dysfunction leading to cardiovascular consequences.

Next slide

Now diagnosis of OSA

Next slide:

See the cardinal features of OSA are loud snoring and excessive daytime sleepiness other complications of hypoxemia, hypercapnia and cor-pulmonale.

Next slide:

Clinical features can be daytime symptoms and night time symptoms. Daytimes symptoms are excess daytime sleepiness, cognitive and memory impairment, executive dysfunction lack of concentration, erectile dysfunction, impotence or decreased libido, dry mouth, gastroesophageal reflux and morning headache.

Next slide:

Sleep symptoms are loud snoring, snorting, non-restorative sleep, awakening with choking, observed episodes of breathing cessation during sleep- this will be witnessed apneas by bed partner, abrupt awakening accompanied by shortness of breath, awakening with a dry mouth or sore throat.

Next slide:

Sleep symptoms are difficult staying asleep, insomnias, nocturnal polyuria, restless sleep, vivid dreams, gastroesophageal reflux, hypersalivation, diaphoresis.

Next slide:

Clinical features are obesity, large neck circumference, narrow mandible, narrow maxilla, retrognathia, dental malocclusion, reduced nasal patency, high and narrow hard palate, elongated and long lying uvula, enlarged tonsils and adenoids, macroglossia.

Next slide:

How will you Assess? - 2 scales are available- Epworth Sleepiness Scale and Stanford sleepiness scale.

Next slide: (Scale)

This is Epworth Sleepiness Scale. Scores are given consists of eight questions 0 to 3, max 24 and score of 11 or above is considered as excessive daytime sleepiness.

Next slide:

Diagnosis is by Polysomnography- This is Gold standard for diagnosis of Obstructive sleep apnea. Alternatives are- partial channel PSG, home monitoring devices, actigraphy. By radiography you can assess the upper airways. By functional imaging and automatic pressure titrating, that is CPAP.

Next slide:

Polysomnography is gold standard. In this there is simultaneous recording of nasal or oral airflow, thoracoabdominal movement, electroencephalogram, electro-oculogram, electromyogram and Oxygen saturation.

Next slide: (Graph)

This is one of the record of polysomnogram. You can see here cessation, these are snoring recorded in this patient.

Next slide:

Polysomnographic studies are expensive. There are not many laboratory here and one night is required for diagnosis and one night required for therapeutic purpose. This can be done by split night studies. The first half of the study night is used for diagnosis and second half to monitor response using CPAP. The split night studies are considered accurate and cost effective.

Next slide:

Then coming to the cardio-respiratory monitoring: This measures only airflow, respiratory effort, oxygen saturation, heart rate but will not be recording EEG. This can be done at home. The advantages are less price, portability and convenience to do at homes.

Next slide:

What is the role of overnight oxymetry? This is a screening test to identify patients who are at risk of having significant OSAH. Should never be considered as a substitute for in-lab PSG or cardio-respiratory monitoring. What are Limitations - inability to detect apneas hypopneas not associated with oxygen de-saturation. Nocturnal oxygen de-saturation may be related to sleep hypoventilation without upper airway obstruction. There are many conditions causing hypoxemia- examples COPD, severe kyphoscoliosis, muscular dystrophy. Therefore, observation of hypoxemia by oxymetry cannot be taken as diagnostic criteria but can only be used as a screening test.

Thank you very much for your kind attention!

Endocrine & Metabolic Aspects: Obstructive Sleep Apnoea

Dr R Goswami

Good Morning to all of you, I've prime interest in Calcium disorders but this is the first time Dr. Bajaj made me interested in Endocrinology of sleep disorders. So I'm finding it really interesting & getting excited also.

1. Endocrine Considerations.

The job is to find out what are the endocrine considerations in OSA. Endocrine disorders can give rise to OSA. OSA can give rise to endocrine disorders & there are certain disorders where you don't know whether it is the OSA which has given rise to endocrine disorders or endocrine disorders which have given rise to OSA. For Eg. – Diabetes, Obesity & Metabolic Syndrome.

2. Upper Airway Structure & OSA.

This part has been covered by Dr. Vijayan very well.

3. Saggital Representation of the pharynx.

This part also what is the mechanism of OSA & how these are affected because in endocrine disorders, many of these are affected.

4. Role of testosterone in pathogenesis of OSA.

What is the primary role of hormones in the pathogenesis of OSA. It's not very clear but the literature tells us because OSA is more common in males & that too in the middle age group. Post Menopause, females are also affected by OSA. So taking this point in view, testosterone has some role in the pathogenesis of OSA. Testosterone replacement can trigger OSA. PCOD Patients: Poly Cystic Ovarian Disease patients who have some hyperandrogenism, also have higher prevalence of OSA. These three point towards the role of testosterone in OSA.

However, there are points against this also. In volunteers with OSA who were given androgen blockade, there was not much improvement in AHI index.

5. Nocturnal Melatonin plasma levels in patients with OSA: the effect of CPAP.

Another hormone which might have some role in the pathogenesis of OSA is melatonin. Normally, there's a peak of melatonin at 2:00 A.M. in the night & this peak is less and delayed in patients with OSA. It occurs at 6:00 A.M. in the morning in patients with OSA.

As you all know that the circadian rhythm is controlled by the suprachiasmatic nuclei, & melatonin secretion is a free running i.e., timely returning by circadian rhythm; not by environment or by biological day or night. So it is primarily determined by circadian rhythm & if you're finding alterations in sleep, then it is an abnormality in the circadian rhythm, giving rise to alteration in melatonin & melatonin induced sleep disturbances.

Levels are not increased after CPAP treatment. This further indicates that melatonin has a primary role & it is unlikely to be corrected by that therapy for OSA which are not directed towards melatonin.

6. Androgen & OSA.

There is a lot of data on hypogonadism in patients with OSAS. It is common in males. There are several studies which have found total testosterone low.

Can give rise to Erectile Dysfunction as mentioned by Dr. Vijayan & yesterday pointed out by Dr. Bajaj.

CPAP therapy may improve total testosterone.

Female patients with OSA have low progesterone.

So hypogonadism is seen in males as well as females. More commonly in males but there is a catch in this. When you measure serum total testosterone, it's not the free testosterone that you're measuring. It's difficult to measure free testosterone. There are no good assays to measure free testosterone. Just like for free T4 and Estradiol, there are no good assays. What you measure is the indices of testosterone by measuring sex hormone binding globulin (SHBG) which is itself dependent on many factors eg. Obesity. So total testosterone, 80% of which is bound to SHBG is likely to be low in obesity. It's assay is resultantly low because of this. So you may get false results in OSA if you just measure total testosterone or if you don't adjust for SHBG. That also is not accurate because after all it's a dry index based on statistics. So we need to have data based on free testosterone in OSA before we can comfortably say that it's low in patients with OSA.

7. The Association of Testosterone.

For eg., if you see this study, this study which came in JCEM , it's a large study, large amount of patients were divided into quartiles based on their serum testosterone levels . None of the indices of OSA; as you see in 1st column, they were different in different quartiles. Trend was seen for all of them so there was no confusion with regard to the exact level of testosterone, whether free testosterone levels are low or not. I'll come to this point subsequently also.

The ED which you see may not be totally because of Hypogonadism. There are several other reasons which may give rise to ED. For eg., disturbed sleep itself, anxiety itself can give rise to ED.

8. OSA & hypothalamic-pituitary-adrenal & thyroid axis.

After androgen axis, there's some evidence that increased response of ACTH to CRH but cortisol isn't impaired. The cortisol levels have been found normal in patients with OSA.

Pituitary-thyroid axis was found normal in these patients. There is increased BNP which is because of increase in intrathoracic pressure & this can lead to higher production of BNP & they can have polyuria because of that. There are reports of patients with OSA waking up several times in night for urination.

9. Hypertension.

There can be hypertension as mentioned by Dr. Vijayan. It is associated with increased Angiotensin-Aldosterone activity & this per say is because of hypoxemia induced increased sympathetic stimulation. So we've reason to say that hypertension which you see in OSAS has some endocrine compartment.

CPAP therapy improves Hypertension but didn't have much effect on Angiotensin-Aldosterone activity. So we do not exactly know what is the primary role of increased aldosterone activity in the cases of OSA syndrome though it's manifestations are affected by in forms of hypertension, they're determined by increased Sympathetic activity & increased Renin-Angiotensin-Aldosterone activity.

10. Obesity & OSA.

Obesity is common in population. Obesity can give rise to OSA syndrome because of the reduction of the upper airways.

OSA can itself give rise to obesity because of increased daytime sleepiness & less activity. There's 10% increase in weight gain leads to 32% higher prevalence of AHI which is an index of OSA.

Most of the patients who are going for bariatric surgery have OSA syndrome. So we've to keep this in mind when we treat patient with bariatric surgery.

Besides simple obesity, it is the distribution of fat. It's not only the BMI, but it is the distribution of fat which is important. There is data which correlates presence of OSA with neck circumference & waist circumference. But then that also is not fully accurate, you've to adjust for visceral fat that also is not accurate because you don't know what is the amount of fat in the pharyngeal tissue. So it is the fat distribution which is important when you correlate OSA with obesity. In a normal person also you can have OSA & that can be a cause of obesity which is localized in the pharyngeal tissue. These parts are yet to be studied. We don't know what is the status & there's no research in this direction...

11. Obesity & OSA.

Dr. Vijayan has adequately pointed out what are the mediators in increased oxidative stress.

Besides there are several adipocytokines which are produced from the adipose tissue & these are named – Leptin, Adiponectin & Visfatin. The studies have found alterations in levels of the hormone in patients with OSA. What is the effect on these hormones after CPAP treatment or what is the effect on Oxidative stress is not known. Several of these hormones have effect on Interleukin & TNG which are considered for the metabolic syndrome from the insulin resistance point of view.

12. Treatment of Obesity & OSA.

After bariatric surgery, OSA may improve but not fully. This is because obesity doesn't completely go & may recur also. There is increased peri-operative deaths because of OSA in patients undergoing bariatric surgery so we have to keep this in mind when we take patient for bariatric surgery.

13. Diabetes & OSA.

There are various endocrine disorders which are attained with OSA & they themselves lead to OSA. For eg., Type 2 DM – There is plenty of data showing increased prevalence of OSA in impaired glucose tolerance or

diabetics with poor glycemic control . Surprisingly, the data is coming which also shows that type 1 DM patients, as they become old , also develop OSA syndrome.

Fatty liver which is a complication of obesity, has been found to be more.

Complications of Diabetes

Micro and macro-vascular complications. There's some data on this, I'll come to this. There's some relationship of OSA with glycemic control in diabetes. Effect of treatment on glycemic control. Some data but not adequate.

14. Type 2 DM & OSA.

For eg., if you see this first graph. This is a compilation of several studies in a meta-analysis in 5000 subjects. There's increased risk of diabetes in patients with OSA. For severe OSA the risk was 1.63 &.....

15. Ctd.

Which had mild OSA, the risk was little less but it was there. So it correlates with the presence of diabetes mellitus in impaired glucose tolerance; correlates with the severity or all & presence of OSA in these patients.

16. Disturbed Subjective Sleep Characteristics in adult patients with long standing type 1 DM.

This is the data I was talking about. This is recent data which has come in 2011. Three times higher occurrence of OSA in patients with type 1 Diabetes seen when they're old. This study was done in older patients with type 1 DM.

17. T2 DM with OSA: CVS & Chronic Complications.

This data which is coming in diabetes that OSA Syndrome can lead to higher 10 year cardiovascular risk in females with diabetes & it has relationship with insulin resistance & insulin secretion.

18. Table 1. Patient's Characteristics.

We concentrate on these red lines. This is data on patients with OSA syndrome & the control diabetics who didn't have OSA. They were matched in terms of age. But obesity & the biggest parameter of obesity, the visceral fat mass was higher in patients with OSA syndrome.

19. Table 2. Cardio-metabolic Profile.

The same table from the same paper shows that the plasma insulin level is higher in these patients indicating insulin resistance.

They had higher prevalence of metabolic syndrome. Almost 100% of them had metabolic syndrome. Fatty liver was higher in these patients with OSA syndrome and 10 year cardiovascular risk was higher in these patients. So when treating DM patients with OSA syndrome, you've to keep in mind that cardiovascular risk is high in these patients & we've to see them again if they've a co-cardiovascular disease also.

20. Laboratory Values.

Third parameter shows the lipid related parameter. Patients had lower apoA-1 which is considered good for hypolipidemia. Higher apoB. The Fibrinogen, uric acid were higher in these patients. Now you can consider on the testosterone, this is interesting study; you find that total testosterone is little low which is even not significant. But if you see the free testosterone, it is higher in these OSA syndrome patients. & why this has become, total testosterone is low & free testosterone is higher which is because of SHBG. SHBG is low in patients with OSA syndrome who had DM. so we've to keep in mind that total testosterone is not the only thing which tells about hypogonadism in patients with OSA syndrome.

21. OSA & Diabetic Neuropathy.

The complications...

22. T2DM with OSA : Chronic Microvascular Complications.

There's data which has come recently in 2012 on complications & OSA syndrome in patients with DM. The Albuminuria & Sight Threatening Retinopathy was higher in patients with OSA syndrome with DM compared to the matched control.

HbA1c was again higher, of course there was some point that duration of diabetes was more in this group 9 vs. 10 but I'm sure they must have adjusted for this when they were coordinating for this because this is highly significant.

23. Mechanism of Diabetes & Metabolic Syndrome in OSA.

There's data on experimental animal. There is a biological basis for all this & the experimental animal if they are sleep deprived & they can have increased Sympathetic activation, reduced insulin sensitivity; they take more diet during the daytime, when they're awake. There's up-regulation of nuclear factor Kappa B. Hypoxia inducible factor 1 is increased.

24. Treatment of OSA & Diabetes.

The Treatment of diabetic patient with OSA with CPAP. This is a limited data but whatever data has shown. Its 3 month data which has not shown any change in HbA1c but of course long term studies are required before we conclude anything from this short study but there's a need for more studies in type 2 DM; to look for the effect of OSA syndrome & relationship with glycemic control.

25. PCOD & OSA.

There's data which is coming PCOD. I've mentioned this earlier that it may be related to the increased progesterone level in these patients.

26. Acromegaly & OSA.

Now I come to the 3rd aspect of endocrinology which is there in OSA. There are endocrine disorders which are clearly associated with OSA syndrome; there's no doubt about that & you can see 70% of patients with active acromegaly have OSA syndrome. Because of various reasons, they've larger jaw, so tongue can back protrude in these patients. They've enlarged tongue & the pharyngeal thickness. Salt retaining effect of GH leads to edema in the pharyngeal wall. Obesity is there. There can be associated central hypothyroidism in acromegaly. There can be myopathy of tongue muscles. So it can give rise to reduction in upper airway space.

27. MRI

This is a good diagram which I could get from JCEM. If you see, these are pre-operative MRI of patient with acromegaly-enlarged soft palate & after therapy, it came down.

This shows that the acromegaly – OSA can improve after therapy but this improvement is not fully because 40% of patients continue to have OSA syndrome after surgery. So we've to keep in mind that patient with acromegaly, they've higher prevalence of OSA syndrome. For me, it is a common illness, because in endocrine day and night we see acromegaly. For you it may be rare so it is important for us that we keep this in mind.

28. GH deficiency, therapy & OSA.

Not only excess of GH can give rise to OSA syndrome. There is data that patients who are GH deficient & those who are getting adequate replacement for all the hormones except GH, they show OSA syndrome. When they're treated with GH in adequate dose, they show improvement in OSA syndrome but when they're over-treated, again they show return of symptoms of OSA syndrome. If we undertreat them, then also they can continue to have OSA syndrome. If we over-treat them, they can also have OSA syndrome because of GH excess.

29. Hypothyroidism & OSA.

These are last few slides. Around 1/3rd of patients with hypothyroidism can have OSA syndrome. The prevalence of OSA syndrome in hypothyroidism is just like that in normal population because both are very common so it is difficult know, whether prevalence of hypothyroidism is increased but I've told you earlier that whatever studies are there, they've shown no impairment in the pituitary –thyroid axis, in patients with OSA syndrome. So this explains the lesser prevalence of hypothyroidism compared to 35% of the OSA in hypothyroidism.

The presence of goiter is an additional fact; which can contribute to OSA, central apnoea because decreased ventilator drive & neuropathy can give rise to OSA syndrome in hypothyroidism...

30. Hypothyroidism Treatment & OSA.

Treatment is invariably successful, so we should always think of hypothyroidism whenever we are seeing patient with OSA syndrome & that their free T4 & T6 measured & treat them adequately before we make a diagnosis of idiopathic OSA syndrome or obesity induced OSA syndrome.

31. Summary.

To summarize, there are hormones which are linked with the pathogenesis of OSA syndrome. For eg., Testosterone, melatonin. Obesity & Adipokines may have independent role but data is needed for this. Hypogonadism can be seen in both males and females. More study is required with regards to free hormones before we can conclude.

There's impaired CRH response. There's more of ACTH but it doesn't have any effect in terms of cortisol level.

Prevalence of OSA is high in acromegaly. It is partially reversible. It is fully reversible in hypothyroidism where there is increased prevalence of OSA.

32. Summary 2.

Hypertension which has some endocrine component can be seen in these patients, metabolic syndrome is increased, T2DM is increased.

The relationship with hyperglycemia & OSA syndrome is to be investigated & there's lot of scope for research for the new generation.

Microvascular & Macrovascular data is coming up that these complications are also increased; we have to continue with the studies in larger cohort.

Insufficient Data on effect of CPAP treatment on HbA1c.

In nutshell, patient with DM should be screened or should be assessed for presence of OSA; because many of these complications are reversible to treat OSA properly.

THANK YOU

Co-Morbidities associated with OSA.

Dr V K Vijayan

My next lecture is Co-Morbidities associated with OSA.

1. OSA and Cardio-vascular Diseases-

The most important co-morbidity of OSA is cardio vascular diseases. OSA has been shown to increase the risk for systemic hypertension, pulmonary vascular disease, ischemic heart disease, cerebro vascular disease, congestive heart failure, arrhythmia. However, a casual relationship remain controversial. The reason, many risk factors for OSA are also known risk factors for cardio vascular diseases. That is, increasing age, male gender and obesity. OSA is also associated with conditions that are known to increase the risk for cardio vascular diseases. Example, diabetes mellitus, hypertension. Therefore, it is difficult to prove whether OSA independently cause cardio vascular disease or not.

2. OSAS and Systemic Hypertension-

The relation to systemic hypertension- Normally, there is a dipping phenomenon in blood pressure that is, in normal individuals, sleep is associated with a reduced blood pressure when compared with wakefulness. Systemic and diastolic blood pressure may decline as much as 10 to 15 percent. Sleep apnea has been found to blunt this dipping phenomenon during sleep. Disordered breathing during sleep has been found to be associated with acute peripheral vasoconstriction and rise in blood pressure during sleep. Several studies have shown that OSA increases the relative risk for hypertension. There are important studies that is, Wisconsin sleep cohort study, sleep heart health study, Canadian population based study, study from Spain. These are most important study Wisconsin sleep cohort study. There were 709 participants. These study has shown there is a dose response association between sleep disorder breathing at baseline and the presence of hypertension 4 years later. This was independent of known confounding factors and this study suggested that sleep disorder breathing is likely to be a risk factor for hypertension. And sleep heart health study, in cross-sectional study, that is involving more than 6000 of patients. This showed a linear relationship between mean systolic and diastolic blood pressure and OSA severity that means, OSA severity increases, blood pressure increases.

3. OSAS and its Studies-

The Canadian population based study had shown, each apneic event per hour increased the risk for hypertension by one percent. Each ten percent reduction in nocturnal oxygen saturation increased the likelihood of hypertension developing by 13 percent. That means, these cross-sectional study, Wisconsin sleep cohort study, sleep heart health study have shown that there is relationship between OSA and hypertension. But in the Logictonus study from sleep heart health study, that is a prospective cohort study of 2470 participants aged more than 40 years without baseline hypertension and not on anti-hypertensive medications. Here again, there is a significant relationship between the risk of developing hypertension and increasing baseline apnea-hypopnea index. However, this association was lost after adjustment for BMI.

Therefore, this Longitudinal study has shown that when we have there is no relationship. But there are some modest influences of apnea-hypopnea index greater than 80 on hypertension. In this study, that could not be excluded. What about the Spain study? This was a study of 1180 individuals, 30 to 70 years of age. This randomly sampled population followed for a 7.5 years for incidental hypertension. The risk of developing hypertension significantly increased the higher respiratory disturbance index. Here again, there is a relationship, but this again lost when it was adjusted for age and BMI.

This is a controversy now. See, most important 2 study of cross sectional study, one, Longitudinal study, and other, cross sectional study, there is a relationship .but there, when the Longitudinal study was taken, there is no relation when adjusted for age and BMI. Again controversy persists. There are all cross-sectional Longitudinal study. what about the interventional study? CPAP is the treatment, when the CPAP has been shown to reduce acutely attenuate sympathetic drive and nocturnal blood pressure in OSA. Observational studies from uncontrolled and highly selected populations have suggested improvements in blood pressure controls with CPAP. A metal analysis of 12 placebo controlled, randomized trials found a statistically pooled reduction in mean blood pressure by 1.69mm, that means, is very low reduction after CPAP treatment. Most of these trials were limited to noimopetal again interventional studies are not contributing much.

4. OSAS and Resistant Hypertension-

What about the resistant hypertension, OSA Resistant hypertension is defined as uncontrolled blood pressure more on 140/90 mm mercury on an optimally dosed three drug regiment, ideally including a diuretic. Then still after giving three drug peripheral vasodilators, that is resistant hypertension. In this hypertension

there has been shown that there is increased levels of aldosterone in OSA. There is a significant correlation between aldosterone levels and severity of OSA. The study was done in forty one of patients with resistant hypertension. In 96 percent of men and 65 percent of women, an apnea- hypopnea index of more than ten. Aldosterone may cause chronic what has been postulated say, is aldosterone may cause chronic parapharyngeal fluid retention that is causing obstruction. That has been suggested CPAP treatment with aldosterone may not be sufficient there may also along with CPAP treatment. That is not conclusive report emerging but the seventh report, there of even there are controversial research from longitudinal intervention studies. The seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure. Now, lists sleep apnea as a significant cause of secondary hypertension. Therefore, it is included in secondary cause of secondary hypertension.

5. OSAS and Pulmonary Hypertension-

Now, what about the pulmonary hypertension? Pulmonary hypertension is defined as a mean pulmonary arterial pressure more than 25 mm mercury at rest or more than 30 mm mercury with exercise as measured by right heart catheterization. The prevalence of pulmonary hypertension is reported to vary from 17 to 52 percent with very variability. However, there are no population based data to know the prevalence of pulmonary hypertension in OSA. In a study of patient with OSA with no clinically significant cardiac and pulmonary disease, there are supposed to call pulmonary hypertension. There was a prevalence of 41 percent. There was no difference in AHI, BMI, smoking history and lung function between patients with pulmonary hypertension and those without pulmonary hypertension. A placebo controlled randomized cross over trial of CPAP and shamCPAP over 12 weeks has been reported in 23 patients. In this study, CPAP therapy reduced pulmonary airway systemic pressure in all patients of OSA, more so in those with pulmonary hypertension at baseline.

6. Role of Reactive Oxygen Species in Cardio Vascular Changes in OSA-

This is the possible mechanism of pulmonary hypertension and systemic hypertension. See when there is Obstructive Sleep Apnea, there will be night time hypoxemia. This cause of hypoxemia and re-oxygenation and reactive oxygen species are produced, there will renin- angiotensin mechanism is involved and this causes systemic hypertension and left ventricular hypertrophy. In some situation when the persistence of nocturnal hypoxemia will lead to daytime hypoxemia as well. This ultimately lead to pulmonary hypertension, right ventricular hypertrophy.

7. Cardiac Arrhythmias and Cardiovascular Mortality-

Now what about the cardio vascular mortality? Sleep heart health study has shown, but compare with subject with respiratory disturbance index of less than 5, those with severe OSA had higher rates of atrial fibrillation, non sustained ventricular tachycardia, ectopic ventricular beats and ventricular arrhythmias. Brady-arrhythmia are also commonly reported in OSA, may correlate with severity and can occur with structurally normal heart. However, a causative role for sleep apnea in serious arrhythmias or sudden death has not been proven.

8. OSAS and Heart Failure-

And with regard with heart failure, there is a close link between OSA and heart failure by their close association with ageing and obesity, .The Framingham study has shown that increasing BMI is directly correlated with incident heart failure, may be mediated in part by OSA. Incident atrial fibrillation ,an important risk factor for heart failure is also associated with the degree of oxy-hemoglobin de-saturation that means , de-saturation, atrial fibrillation, cardiac failure . This is a very important study because there are five groups here

9. Men with Fatal CV Events (more than 10 years follow-up)-

One is control , the other one is snorers without OSA ,third one is mild OSA sever OSA, this is OSA patient treated with CPAP. This is ten years follow up study,fatal cardiovascular events . You can see here the patient with mild OSA , snorers and those treated with CPAP ,there is significant reduction in mortality .those patients OSA who are not treated with CPAP , you can see here as time passes mortality increases .This clearly shows cardiovascular mortality is more in those patients .See OSA patients who are not treated with CPAP, when they were treated with CPAP ,there is significant reduction in cardiovascular mortality.

10. Men with Non-Fatal CV Events(More than 10 years follow-up)-

And what about the other non fatal cardiovascular defects?Even in non disorder , study in males in even

in the non fatal cardiovascular events , the subject not having OSA, non treated with CPAP, there is reduction in mortality and there is a high mortality and CPAP treatment significantly reduce the effect. These are the studies in male.

11. CV Mortality in Women with OSA with or without CPAP Treatment-

What about the females ?If you look at the females, you can see here again this is classified into controlled and various mild and moderate. This is severe OSA in females, moderate, mild, OSA in females and there are all severe, mild patient, treated patients. Significant reduction in mortality. Severe OSA in females and mild and moderate not treated with CPAP, there is a increase in the mortality rate. Where as CPAP treatment significantly reduce. Therefore both males and females, CPAP treatment is reduce mortality with on follow-up. There are showing severe OSA is associated with cardio vascular death in women and adequate CPAP treatment may reduce this risk.

12. OSAS and metabolic Syndrome-

Now, OSAs and metabolic syndrome. OSA has been independently associated with metabolic syndrome. It has been suggested that OSA may contribute to the development of metabolic syndrome. Chronic intermittent hypoxia and sleep deprivation with sleep loss may play a role in trigger inflammation. OSA may be a risk factor for metabolic syndrome.

13. Components of Metabolic Syndrome-

These are components of metabolic syndrome, abdominal obesity, insulin resistance, hypertension, low serum high-density lipoprotein, elevated serum triglycerides. Three of these five should be present to diagnose metabolic syndrome.

14. Features associated with Metabolic Syndrome-

These are features associate metabolic syndrome, pro inflammatory state, pro thrombotic state, hyperleptinemia, hypo adiponectinemia, endothelial dysfunction, micro albuminuria.

15. OSAS and Type-2 Diabetes Mellitus-

Already Goswami has talked about diabetes, I'm not mentioning.

16. CPAP for Metabolic Syndrome-

Now this a study form India. That's why I'm putting it, this is by All India Institute of Medical Sciences on metabolic syndrome. In a double-blind placebo controlled randomized trial, patients were treated for Obstructive Sleep Apnea syndrome with three months of continuous Positive Pressure followed by three months of shamCPAP or vice-versa, with a wash period of one month in between.

17. Study Overview-

This study has shown CPAP therapy lowered blood pressure and ameliorated metabolic abnormalities.

18. OSAS and Incident Stroke-

What about a stroke?

The incidence of stroke was studied in a geographically diverse, community based sample of male and female participants in the sleep heart health study, a multi-center prospective study. Based on 8 years of prospective data from the study, it has been observed that modest to severe levels of sleep apnea are associated with an apporoximately three fold increased risk of ischemic stroke in men.

19. OSAS and Neurocognitive Diseases-

The remaining neuro-cognitive deficit. Neuro-cognitive deficits occur with a high frequency In OSA. These deficits can affect any cognitive domain including learning, memory and attention. It has been suggested that severe sleep apnea can increase the risk of dementia in the elderly. The impaired mood, reduced vigilance, impaired concentration, reduced memory, impaired performance in surgical skill- there are -for dr -is performance surgical skill, anesthesia administrating intubation and EKG interpretation.

20. OSA and Erectile Dysfunction-

And OSA, erectile dysfunction is common in patients with OSA. In a prospective study of non diabetic men under the age of 60 years with newly diagnosed OSA, erectile dysfunction was reported in 45.6 percent and 27.2 percent had diminished libido. The oxygenation nadir that is lowest oxygenation - saturation--- has the greatest association with the development, therefore there is a relationship between hypoxemia and erectile dysfunction. Treatment of OSA with CPAP has been found to improve erectile dysfunction.

21. Other Medical Consequences-

That are some other medical complications, daytime sleepiness, loss of alertness, deficit, reduced vigilance, impaired executive function, there will be increased risk for automobile and occupation accidents, this also important because of drivers, more accidents. You are all aware of the plane accident Bangalore, what has to be reported, that pilot was sleeping, therefore the OSA may be the contributory factor. Therefore, this is, we have to be, again very careful, we have to do with OSA in decreased quality of life.

Thank you very much.

Childhood obstructive sleep apnea

Dr. R. Dayal

Introduction:

Dr Mohankumar, Dr Misra director of the AIIMS here Dr.Rajkumar director of AIIMS Rishikesh, my fellow speakers friends , ladies and gentlemen.

I am most grateful to Prof. Bajaj for giving me this opportunity to come here. In fact my job has been made very simple by Dr.Vijayan. Who has covered most of OSA and the only objection I have to him is that he stole away my Tajmahal which belongs to Agra. For the information of Prof. Mohan Kumar may I mention sir, that the INDIAN ACADEMY OF PEDIATRICS, woke up, although very late to realise that the sleep problems in children are being grossly neglected. And in the year 2011 they formed an IAP sleep cell and may be the national convenor for this program. In the last two years we have been conducting workshops across the country to familiarise paediatricians about the growing number of sleep disorders and how sleep disorders shape a child's personality. And lead to poor school performances etc etc....

Sleep Disordered Breathing:

This has already been covered that how sleep disorder breathing has a spectrum of primary snoring, UARS and sleep apnea.

Sleep Apnea:

Apneas represent the complete cessation of airflow and of three types

- Central apnea
- Obstructive and
- Mixed.

This again has been adequately covered. So I would be focusing on those areas which are relevant to paediatrics.

Sleep Disorder Breathing: Epidemiology

Very few studies exist in the Indian literature on childhood OSA and in fact Childhood Sleep disorders. And this incidence varies from 1-3% in the children of preschool age in most western studies. In the few studies that have been conducted in India. Among the urban children, incidence was found to be about 5% of all sleep disorders. That means OSA is a part of all sleep disorders. And these are the two studies worth mentioning. One is by Suri et al. in the Indian journal of sleep medicine in 2008 and another one by the Bharti et al .In Indian paediatrics in 2006. Of course according to the literature sleep disorder breathing is more common in African, American and Asian children.

Prevalence of Snoring/ OSAS:

A very nice study was conducted by Dr.Parmesh in Bangalore. And this was the part of the thesis submitted by one of his candidate for the DNB examination in 2010. In which they looked at about nine hundred and fifty (950) Children aged from 2 to 17 years. And found that primary snoring was present in 8 and obstructive sleep apnea in about 1% and when they analysed the causes for sleep disorder breathing, they found that adenoid hypertrophy was present in 50% children, allergic rhinitis in 58% Asthma in 35% .Adenoid hypertrophy and asthma in 7.9%, adenoid hypertrophy in 5.2% along with allergic rhinitis and asthma. This is the break up in the various age groups.

Toddlers having 21% the preschool children having 26.3%. Most was in school going children that is 44% and the adolescent with about 7%.

Description Of OSA Event:

The description of OSA event just to revise has decreased alveolar ventilation. Decreased alveolar ventilation leads to decreased alveolar po₂, increased alveolar pco₂. Decreased arterial oxygen, increased arterial pco₂.And of course leading to arousal and partial awakening.

Why Obstruction occurs during sleep:

Now why does obstruction occurs during sleep. it is the supine position and control of breathing during REM sleep where there is lack of 'wakefulness' drive.

A decreased tone of pharyngeal muscles, depressed reflexes, including pharyngeal dilator muscles. Decreased tone of intercostals and accessory muscles, depression of minute volume and depression of response to hypoxia.

Anatomic factors that predispose to OSA:

The anatomical factors have been mentioned but a word about paediatric age group is that we have lots congenital anomalies. Which can lead to anterior nasal stenosis, caudal stenosis, congenital choanal stenosis, is a well known entity, DNS and seasonal perinitis and nasal polyps which can lead to obstruction at this level

Nasopharyngeal and oropharyngeal causes include the most important adenotonsillar hypertrophy, macroglossia found very much in hyperthyroidism which is an entity being increasingly recognised in Indian children cleft palate and flap repairs. Craniopharyngeal abnormalities like micrognathia and Pierre Robin Syndrome. Midface hypoplasia and down syndrome and again mandibular hypoplasia and again Pierre and Robin syndrome.

Functional factors that predispose to OSA:

Functional factors in children that predispose to OSA of course is the REM sleep related pharyngeal hypotonia. Abnormal neural control generalised hypotonia in down syndrome, CNS injury birth asphyxia. With all these fancy NICUs coming up across the country. We have lots of children surviving who have had HIE hypoxic Ischemic encephalopathy in the time of birth and that can again contribute to this. Brainstem dysfunction, Chiari malformation. Drugs which can again contribute to OSA is here. Among the other causes obesity is one which is being increasingly recognised now and a word about it which I shall just talk a little later.

Atopy and OSA:

Atopy and OSA in large number of studies in adults with atopy there is high prevalence of snoring. A significant association between asthma and snoring this effect is independent of upper respiratory tract symptoms, cigarette smoking and race has been found in children. Again I will mention that asthma is on a very heavy increase in the Indian population in children. Atopy is now recognized as an independent risk factor for snoring.....

Risk factors:

These are of course the risk factors male sex, African American race, recurrent otitis media, asthma, tobacco smoke and a past history of prematurity.

Obesity and OSA:

The classic presentation of children with OSA as underweight children with adenotonsillar hypertrophy is being substantially replaced now by young patient who are either overweight or obese. For every 1kg/m² increment in BMI beyond the mean BMI for age and gender the risk of OSA increases by 12%. In the obese children upper airway narrowing results from fatty infiltration of the upper airway structures promoting pharyngeal collapsibility. Again obesity reduces 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. Obesity is associated with peripheral and central leptin (an adipocyte-derived hormone) resistance, which in turn can lead to relatively ineffective elevation of circulating leptin levels thus, reduced bioavailability of leptin resulting in altered ventilator responses may also play a role in interaction between obesity and OSA. Ahh it has again been shown that the central drive the ventilatory central drive is blunted in children with obesity.

Symptomatology:

The OSA manifestation can be classified into the sleep related ones, daytime ones and neurobehavioural ones. this is again in special reference to children.

Sleep related symptoms:

Many children who snore do not have OSA I emphasise this because a misconception exist that whenever they find a child snoring. oh well he has OSA that's not the story but very few children with OSA do not snore. The breathing pauses are there, choking or gasping arousals which may result in nocturnal awakening, but are more likely to cause fragmented sleep. restless sleep, diaphoresis, enuresis because of the disruption of ADH and unusual sleeping position. Children with OSAs have very unusual sleeping position that they can keep their neck in hyper extended just that the airway remains patent.

Daytime symptoms:

Morning headaches due to cerebral vasodilatation because of CO₂ retention. Excessive daytime sleepiness (EDS) which can be evaluated by various scores. And the teacher complaining that the child falls after school. Falls after sleep while at school. A dry mouth, chronic mouth breathing and a poor appetite.

Neurobehavioral symptoms:

Neurobehavioral retentions symptoms, now the most important one is here. Deficits in attention most with SDB do not present with daytime sleepiness and are more likely to be hyperactive or inattentive often being diagnosed with ADHD. That is attention deficits hyperactive disorder and this a fact in fact we had this child. who was being treated for ADHD with all these drugs etc etc. Coming from very affluent family and in fact he did not have ADHD. The only problem he had was obstructive sleep apnea leading to his fragmented sleep which made him very jumpy and with full symptoms of ADHD. Memory deficits, mood disturbance, subjective sleepiness and of course poor school performance.

Signs of OSA:

The signs of OSA have been described but no abnormality while awake however long-standing patient the children may develop arterial blood gases they may show metabolic alkalosis. Systemic hypertension, pulmonary hypertension, polycythemia, cor pulmonale, and bradycardia.

Criteria for diagnosis of OSA: apnea-hypopnea index (AHI):

The criteria for OSA is very much the same which has been discussed earlier. And with an AHI less than 5 it is no and of course as it moves severity increases.

Diagnosis of OSA:

The following triad of symptoms is highly suggestive of OSA in children, snoring, nocturnal breathing difficulties and, witnessed respiratory pauses.

Overnight oximetry :

Overnight oximetry. I do agree that it's not a substitute for Polysomnography but yes it measures the oxygen saturation and provides the pulse rate data. The falls and rises in the oxygen saturation are regarded as dips. And the ODIs are suggestive of OSA.

Polysomnography :

Polysomnography which is now regarded as the Gold Standard and the variables assessed are already been discussed. Now a word about polysomnography in children. Imagine if a child tied up with all this and being measured in a polysomnography machine. One year ago we started with a thesis with one of our residents, and she would come back that sir as soon as we tie up the child like this, he jumps up and wakes.

So it is easily said the polysomnography is a gold standard but not easy to do it in children. And we have been able to do it in about ten children so far in last one year but the results are equivocal.

Normal polysomnograph:

This is of course has been shown how a normal polysomnograph looks like.

Obstructive sleep apnea:

This is what it looks like in an OSA

Other investigation:

The other investigation must include a lateral neck radiograph. A very simple thing to evaluate the size of the adenoids which is a very important cause in children. Complete blood count because polycythemia does exist in children because of chronic hypoxia. And of course these tests.

Pharmacologic management:

The management for simple things for example for nasal obstruction due to reduced snoring topical nasal steroids have been tried with benefits. Steroids and antibiotics in the acute management of infected pharyngeal tissues which have compromised upper airway patency. And nasal decongestants for allergic rhinitis. Which is on a very high rise in Indian children.

Surgical treatment:

Surgical treatment. In the majority of children with paediatric OSA, adenotonsillectomy is the first line of treatment. A word about this, many years ago in fact few years ago. Adenotonsillectomy was supposed to be avoided in children. And was said that try and postpone it as far as possible because the adenoids and the tonsils are very important part of reticulo-endothelial system. And they prevent infections in children. So if you get them out at an early age you'll be making a child very prone to infections. But that thinking has of course changed. With a high incidence of OSA stepping in and as soon as it is diagnosed that the adenoids and the tonsils are the culprits involved in OSA. They should be got out otherwise their presence is going to lead to more harm than any good. The reported cure rates post adenotonsillectomy include are range from 75-100% in normal healthy children.

Other treatment modalities:

What is important to remember is that even a children with comorbidities. If adenoids and the tonsils are the culprits they should be removed and those comorbidities should not be considered as a hindering factor for getting the tonsil out. Life style modifications things like very simple things attaching a firm object, such as a tennis ball to the back of a sleep garment to prevent the child from sleeping in supine position. So that he lies in the prone position that keeps the airway open. And he is better off. Weight loss of course. Oral appliances with for CPAP. And surgical option of course do exist.

CPAP (nasal CPAP/BIPAP):

CPAP is the most common treatment in adults but can be used in children and adolescents. Where the removal of tonsils and adenoids is not indicated. Where there is residual disease following adenotonsillectomy. And their major risk factors not amenable to treatment with surgery like obesity and hypotonia. CPAP delivers of course humidified and warmed air through an inter phase that, under pressure effectively splints the upper airway open. These are the various type of appliances which are available.

Obstructive sleep apnea:

This is just to show that how CPAP keep the airway patent here which has collapsed here.

Tracheostomy:

In very severe cases Tracheostomy has been resorted too. If the severe respiratory obstruction is present in both wakefulness and sleep. When there is vocal cord dysfunction, impaired swallowing, or absence laryngeal protective reflexes. And may be necessary for severe OSA complicated by cor pulmonale or where CPAP is unsuccessful or not tolerated. The alternative surgical measures are reconstructive surgeries.

Diagnostic approach to a case of snoring:

To conclude, the diagnostic approach to a case of snoring. Let us remember that primary snoring is more common than obstructive sleep apnea. And every child who is snoring does not have obstructive sleep apnea. So child who has snoring as suspected sleep disorder breathing- If he has arousals and witnesses several difficulties. Yes of course this is the line and if there are no arousals and if there is no witnessed breathing difficulties, he just has primary snoring. If he has arousals and witnessed breathing difficulties. Do a pulse oximetry and PSG. If the arousals present but no ventilatory abnormalities it is just upper airway resistance (UARS) . If arousals and ventilatory abnormalities are present, it is OSA.

Management approach to a case of SDB:

So once it is a diagnosed case of SDB. If it is primary snoring treat underlying cause, change the sleeping positions and apply oral devices. For UARS treat underlying cause. If it is OSA, yes treat the underlying cause and adeno-tonsillectomy, CPAP, tracheostomy, surgery etc.

Thank you:

Management of Obstructive Sleep Apnea

Dr V K Vijayan

Treatment of OSA consists of weight reduction, lifestyle modification, Continuous Positive Airway Pressure (CPAP), Bilevel Positive airway pressure (BiPAP), Oral appliances i.e. to keep upper airway open are: Medical therapy and surgical therapy

Treatment depends upon the severity of the sleep disorder breathing.

People with mild apnea have a wide variety of options.

People with moderate severe apnea should be treated with nasal continuous airway pressure. This is the first line of treatment.

Obesity is a major predictive factor for OSA.

Weight loss should be recommended to overweight patients with OSA.

Loss of body weight as little as 10% is associated with clinically significant improvement (26%) in apnea-hypopnea index.

Long term effects of methods of weight loss (Bariatric surgery and carbohydrate restricted diets) are not assessed in longitudinal studies. There are some case reports and observational studies which are coming up.

The Benefits of weight reduction:

1. Decreased respiratory disturbance index (RDI)
 2. Lowered blood pressure
 3. Improved pulmonary function
 4. Improved sleep structure and snoring
 5. Possible reduction of optimal CPAP pressure required
- Avoidance of alcohol for 4-6 hrs. prior to bedtime
 - Avoid using other sedative known to make apnea worse
 - Smoking cessation; smoking increases the risk of snoring and apnea
 - Sleeping on one's side rather than on the stomach or back
 - Avoid sleep deprivation

These are the lifestyle modifications.

There are three types of medical devices available for treatment:

1. Continuous positive airway pressure (CPAP): Standard treatment for OSA.
2. Bilevel positive airway pressure (BiPAP)
3. Oral appliances (OA)

For treatment of OSA we should start from least invasive and effective to most effective to most invasive and effective.

The least invasive therapy, i.e. Offer nasal CPAP therapy is given first to all patients.

Patients with mild to severe OSA who refuse or reject nasal CPAP therapy, are offered BiPAP.

If BiPAP fails or rejected, offer OA therapy.

OA can be first line therapy in mild OSA, if they are unwilling to try CPAP that means OA can't be tried in moderate to severe cases, only in mild cases if they refuse CPAP treatment.

Up till attempt all interventions to improve tolerance to CPAP before deciding its failure

Surgical options are offered only if all non-invasive medical therapy i.e (CPAP, BiPAP or OAs) has failed. Therefore surgical therapy should not be given at first.

Which are the guidelines for CPAP treatment?

CPAP in continuous positive airway pressure i.e. a pneumatic seal keeps the airway open during inspiration and expiration by a fixed pressure.

All patients with an apnea-hypopnea index (AHI) greater than 15 (moderate to severe cases) are eligible for CPAP, regardless of symptomatology because of increased risk of cardiovascular morbidity i.e. whether we have symptoms or not moderate to severe case of OSA should be prescribed CPAP because these patients have got increased risk of cardiovascular morbidity

CPAP when there is a mild form of OSA that is OSA 5-14.9, these patient has one of the following

symptoms i.e. excessive daytime sleepiness (EDS), hypertension, or cardiovascular disease you can prescribe CPAP i.e. mild OSA patient with symptoms we have to prescribe CPAP; moderate to severe patients even with not symptomatic to reduce the morbidity of OSA you have to prescribe CPAP treatment.

How to titrate CPAP pressure, because I told that fixed airway pressure is given to the patient to keep the airway open during inspiration, expiration which is done by a polysomnography night study. Pressure is titrated.

Titration is usually done by trial and error method, because there is no fixed way we can give that this is the pressure required. With each patient you have to determine the pressure required for the patient by a trial and error process, adjusting the applied pressure until those respiratory and sleep parameters considered to be clinically important are reduced to the degree to be acceptable. Therefore whatever the respiratory and sleep parameters they are clinically important they should be reduced by the pressure what you are applying That's why this has to be done by trial and error pressure method when after finding out the pressure that is the one prescribed to the patient for treatment at home.

What is the outcome of CPAP treatment?

Optimal treatment of OSA with CPAP

- I. Corrects OSA first. First will be corrected obstruction.
- II. Then correct the upper airway resistance syndrome
- III. The last one is the snoring will be corrected. Not that the snoring will be corrected first.

If snoring is corrected first in CPAP there is something wrong with the applied pressure or if there is sometime what will be happening is there will be leak. That leak will be detected as noise the polysomnogram that will be detected as snoring. Therefore if snoring is corrected first in CPAP treatment you have to check your device and also find what is the defect

If in CPAP treatment OSA should correct first.

If all 3 problems are not eliminated, symptoms can recur. Therefore there will be recurrence of symptoms Then I told fixed CPAP. what is the fixed CPAP? We have told that fixed pressure will be applied everyday every hour to the patient continuously. But the problem is it is a dynamic process, therefore 1 fixed pressure may not be correct always therefore autotitrating positive air pressure is being developed

Fixed pressure CPAP therapy is effective in most patients with OSAH

However, the application of a single pressure value over time has potential drawbacks because the collapsibility of the upper airways varies not only during a single night but also long term therefore night also it varies and long-time also it varies. There are few prescribed fixed pressure but it will not be correct. Therefore auto titrated pipette are there in this device this modifies the applied pressure in real time, according to that required to maintain upper airway pressure It's the real time. It adjusts the pressure what is required for keeping airway open. Therefore this is auto titrated pipette.

In theory, at any given time these devices apply the lowest effective pressure.

Effectiveness of CPAP therapy is:

Adequate levels of nasal CPAP because it is better to be nasal because we cover all the amount it will be a problem. It resolves obstructive apnea and/or hypopnea. It improves oxyhemoglobin de-saturation, and snoring from sleep.

It results in adequate sleep continuity and improve daytime sleepiness, mood, cognitive function in people with both mild and moderate apnea.

CPAP has also been shown to decrease blood pressure, as shown by some of the studies, primarily in patients with severe OSA

It improves the left ventricular ejection fraction in patients with congestive heart failure and OSA.

CPAP plus antihypertensive medication may synergistically improve systematic hypertension

It improves right sided heart function and pulmonary hypertension

CPAP is associated with a lower risk for heart disease, stroke, and diabetes

CPAP has also been shown to increase quality of life

Decreases health care cost and reduces mortality in OSA.

The main problem with CPAP therapy is the compliance. CPAP has to be applied continuously to a patient during all time on long term basis. Nobody is willing to use that. It is a mechanical device applied to most of the patients during sleeping time. Therefore compliance is the big problem.

The use of CPAP > 6 hrs. decreases sleepiness, improves daily functioning, and restores memory to normal levels.

However adherence to CPAP therapy; what is definition of adherence to CPAP. This defined as CPAP

therapy more than 4 hrs. nightly 5-7 days a week. Therefore minimum 4 hrs. per day for 5-7 days a week should be they are taking that is being defined as compliant to CPAP therapy.

46 to 83% with obstructive sleep apnea have been reported to be non-adherent to treatment. Therefore non-adherent to treatment is a big problem in CPAP therapy treatment.

How will you improve the adherence to CPAP therapy?

One is humidification. You can humidify the airway

There are some machine devices available now: Bilevel CPAP is one. See continuous CPAP pressure is applied during fixed pressure during inspiration expiration. In bilevel CPAP during inspiration is more pressure, expiration is less pressure. Therefore pressure will be varying with inspiration, expiration that is both inspiration, expiration. Then auto-CPAP. Auto-CPAP is developed to vary and optimize the level of CPAP throughout the night. Then another one is flexible CPAP i.e. alternates airway pressure between exhalation and inhalation on a breath-by-basis to improve patient comfort.

These are the modalities that have been designed to improve the adherence to CPAP therapy.

Then there may be behavioural interventions, cognitive behavioural therapy that can also tried to improve compliance to CPAP therapy.

Now it is the latest publication so it is being developed some CPAP adherence tracking transmission systems is being developed. This CPAP therapy is being done at home.

See using the smart cards (SD cards) memory stick or wireless transmissions to record the snoring, how many hours they are using it, is there any leak in the system, all will be recorded and we can find out whether the patient is individually using the CPAP properly. Data that they tract can be utilised for adherence, leak, efficacy and flow signal. Now this is an experimental stage and soon it will get the result.

What are the complications of CPAP?

There is a sensation of suffocation, claustrophobia, difficulty exhaling, inability to sleep, musculoskeletal chest discomfort, aerophagia and sinus discomfort, very rarely pneumothorax and/or pneumo-mediastinum. There will be noise and this may lead to spousal intolerance.

Then when you prescribe BiPAP what are the?

CPAP delivers a constant pressure during both inspiration and expiration

BiPAP permits independent adjustment of the pressure delivered during inspiration and expiration.

BiPAP is used in patients:

- I. Who can't tolerate high CPAP pressures
- II. Who have barotrauma complications e.g. ear infections, bloating
- III. If the CPAP level needs to be increased above 15 cm of water. When higher CPAP level is required the use BiPAP.

It has no distinct advantage over CPAP therapy. Therefore CPAP is the first one. There are some situation come then you can use BiPAP.

Then next mechanical device is Oral Appliances

Patients with mild-to-moderate OSA:

1. Who prefer oral appliance to CPAP devices. ? if we prescribe CPAP these mild to moderate patients may decline. Then you can apply the oral appliances.
2. Who don't respond to CPAP therapy.
3. In whom treatment attempts with CPAP failed
Who refused to treat, who failed they can be prescribe oral appliances.
Should not be considered effective therapy for patients with severe OSA. In severe OSA patients you should not prescribe oral appliances.

Oral appliances act by moving the tongue forward. Tongue is being pulled forward that mean increasing the upper airway diameter or moving the mandible and soft palate anteriorly. Again improving the upper airway diameter.

These devices enlarge the posterior airspace. For that multiple different devices are available

There are 3 basic designs that are used to treat sleep related disorders.

- I. Mandibular repositioners i.e. it is anterior movement
- II. Tongue retaining devices again that will not fall backwards
- III. Palatal lifting devices

These are the designs available as oral appliances

More than 40 OAs are available to manage sleep related breathing disorders and obstructive sleep apnea

There are some contraindications to oral appliances:

- When the teeth are less
- Patient is unable to protrude the mandible forward and open the jaw widely. Then you can't apply it
- Pre-existing temporomandibular joint problems, you can't apply
- Severe bruxism
- Patients with full dentures.

These are the contraindications for using oral appliances.

There are some complications to oral appliances

There will be excessive salivation.

Dental misalignment with bite change and tooth movement

Temporomandibular joint disease

Myofascial tooth pain, gum irritation, salivation, Temporomandibular joint sounds

Tongue pain

Patients may also object of having an appliance in their mouth throughout night.

Those are object put in the mouth, they may object that one.

Now coming to the medical therapy. There are many pharmacological agents.

And I have already told about all these things in morning but I am going only to two things. One is endocrinological disorders. There are many types available but none of them are been proved to be useful in treatment of OSA

Thyroid hormone replacement myxoedema. If you replace it with thyroxine it will be a treatment of OSA or growth hormone suppressants. These are the indications for treatment.

Next one is wake promoting agents, modafinil. See what is the role of Modafinil in the treatment of OSA. See now a days what is happening is when a patient comes OSA and excessive day time most of the time, i am not saying always, most of the time Modafinil is prescribed. That is not correct. There are specific indications.

Despite treatment with CPAP, see you have to give CPAP treatment first in a OSA patient.

Despite giving treatment many patients demonstrate residual sleepiness. Optimal pressure is given. Even in some patients residual sleepiness will persist.

Modafinil is a wake promoting agent which has been approved for the treatment of narcolepsy.

In a randomised, double blind, placebo-controlled parallel group trial, Modafinil has significantly improved daytime sleepiness, but has no effect on AHI.

Adult patients with OSA having excessive somnolence despite well treated with CPAP indications. Therefore modafinil in OSA should be prescribed only in those individuals who have been treated with CPAP and despite treatment with CPAP if they have got somnolence persisting, these are the individuals who should be on modafinil, not for every patient diagnosed with OSA.

Then coming to other medical therapy.

One is supplemental oxygen, i.e. there is hypoxemia when there is persisting hypoxemia i.e. one of the problems for many organs because every organ in body requires oxygen when there is lack of oxygen so many problems occur therefore supplemental oxygen therapy improves oxygen saturation level but does not improve airway patency.

Then therapies intended to improve nasal patency because we already talked in children that nasal PSA improves OSA, coexisting rhinitis may benefit from the use of nasal corticosteroids.

Positional therapies.

If you lie on supine position tongue will fall back therefore recommended to sleep on side.

There are some surgical treatments, i just go through

One is Tracheostomy. This is one of the treatment modalities started initially, but now a day it is not being practised, tracheostomy. But when there is a severe patient not controlled with any of these modalities then persistent hypoxemia there will be some indications in some of the patients, not all patients.

Adeno-tonsillectomy again for children.

Procedure for nasal obstruction

Septoplasty

Nasal polypectomy

Radiofrequency ablation of turbinates

Now i didn't have any of these experiences with the surgical treatment .i am just putting forward.

Reduction of soft palate redundancy i.e.

Uvulopalatopharyngoplasty

Uvulopalatal flap

Palatal advancement

RF ablation of the soft palate

Reduction of the bulk of the tongue base to prevent hypopharyngeal or retrolingual obstruction i.e.

Genioglossal advancement

Hyoid suspension

Partial glossectomy

Tongue RF ablation

Lingualplasty

Maxilla-mandibular advancement

There may be laryngeal procedure: Epiglottoplasty

Bariatric surgery i told some very obvious result even though it is not proved

Now coming to the recent advancement. One of the most important thing is as shown the genioglossas muscle which is one of the important muscle that keeps the upper airway open and hypoglossal nerve is supplying that one.

In study of 30 middle aged persons with OSA who could not tolerate CPAP, Implantation of a neuro-stimulator and respiration sensing lead under GA. This stimulating lead is placed on hypoglossal nerve to stimulate the nerve during stimulation. Therefore there will be contraction of genioglossas muscle keeping the upper airway patent.

Therefore this is the one of the modalities being tried now. There will be progressive increase in inspiratory flow with increase in stimulation intensity produced in opening of airway.

This is again an experimental step, this is one of the modalities being tried out now.

Now what i have mentioned is mainly CPAP is the most important treatment. There are 3 mechanical devices CPAP, BiPAP, Oral appliances.

First CPAP, if fails then BiPAP. Oral appliance is last. In mild forms of OSA, if there are decline in CPAP give oral therapy. Surgical is the last one. And this is the latest one hypoglossal nerve stimulation.

Thank you very much.

SLEEP AND STROKE

Dr. MV Padma Srivastava

INTRODUCTION:

Most strokes are caused as a multifactorial processes because of multiple risk factors chief amongs to which are hypertension , diabetes, dyslipidemia, heart disease , smoking and you know those, but there is a emerging evidence that there is whole load of known conventional risk factors which may also be as a cause of stroke occurrence and this knowledge is important because it'll act to a armamentarium for stroke prevention and one of this is obstructive sleep apnoea in fact the role of sleep apnea disorder in circulatory, regulatory as a disrregulatory mechanisms and vascular injury is an emerging concept ;is a developing concept.

CIRCADIAN VARIATIONS IN INFLUENTIAL IN A CIRCULATORY AND VASCULAR PHENOMENON:

There are a lot of physiological functions which go altered when there is a problem in sleep-wake cycle because these functions are their in circulatory system they are altered by the circadian rhythm with for reaching ramification because they occur in a chain like reactions some of them are listed here which include endocrine secretions , thermoregulation, renal functions , respiratory control, heart rhythm ,haematologic parameters , immune system ,drug metabolism .And a lot of it has already been discussed extensively and wonderfully in the previous lectures...

NEXT SLIDE:

So for stroke, let's focus on few small things there is increase in plasma catecholamines levels some where between 4am to 6am in the morning till one noon , there is decrease in fibrolytic activity , increase platelet agreeability that's why you have , what are called as wake up strokes in fact 25% of all acute ischemic events are known to happen when patient is waking up so also we do have heart attacks so there is Load of lot of cardiovascular morbidity and strokes which are happening when a person is waking up, and these are probably...

OVERVIEW:

Some of the reason which have been implicated and...

SLEEP APNOEA:

I am skipping lot of slides because these are already been covered. We know that there is a huge prevalence of obstructive sleep apnoea in fact they say 20% of the population ,one in five and we are unique in the present circumstances that we are ageing so we have lot of ageing population and we are also growing in our waist line therefore both ways I think we are going to see more and more sleep apnoea problems in the coming few years...

WHO SNORES MORE MEN OR WOMEN?

And snoring; I am not going to get into that also just to recap that a snore is that loud vibratory sound which is a respiratory effort in further sleeping individual.

SNORING:

So as regard snoring and sleep disorder breathing again we have been extensively being taught ,so more of that recap but there is a lot evidence which is linking this sleep disordered breathing with cardio vascular morbidity , cerebrovascular accident and they are dealing with stroke one point in snoring ,there is one literature which has said for some there is not extensive but little bit of it has said in fact in this vibratory noise there are these atherosclerotic plug in the carotid artery system which also get dislodged.

SDB AND STROKE:

I do not know what evidence we do have but we do have some evidence of CI in breath that is carotid intima media thickness. I'll come to it a little later so this is circumstantial evidence which points to a causal association with sleep disorder breathing. The rubric under which we are talking of mainly of obstructive sleep apnea and stroke...

SNORING:

The study from Japan where they looked into these patients with OSA and after controlling with this confounding variables which are very many a lot of widespread risk factors and they did find the carotid intima media thickness that's a little kind of biomarker which is correlated with vascular outcome so we have had statins study on CIMT. We had the study it's sort of anti-hypertensive like ACE inhibitors with CIMT similarly they looked at CPAP. I looked at CIMT thickness and they found that they are decreased so this little bit of evidence which is not in favor of that

TYPES OF SLEEP APNOEA:

Again I am skipping this, these two and also these diagrammatics. Sorry because there has been an overlap, so I don't want to waste time on what you have already been taught.

EPIDEMIOLOGY OF OSA:

Now besides the OSA being so very prevalent in the general population, we also know that the commonest sleep disorder breathing which happen in the patient with a stroke is also OSA. So the prevalence of a sleep disordered problem and sleep problem in general in stroke are humongous and they vary from 50% to 70% that's almost 3/4th of patients with strokes have some sleep related issue but OSA is known to predate a stroke, happen at stroke and continue to exist after stroke.

HOW OSA IS MEASURED?

This measurement again I am skipping.

SYMPTOMS/SIGNS OF OSA:

Also the symptoms and signs, you all know very well.

UNTREATED OSA INCREASES YOUR RISK:

Now the untreated OSA we have seen, the morbidity associated with this and there is a huge spectrum.

OSA AND STROKE:

Now why is OSA related to stroke. Now there are shared risk factors. You know that age is the biggest risk factor. We have this metabolic syndrome, we have hypertension which is increasing. It's now said that almost one in three of adults are hypertensive, one in five are diabetics and we have this one in five who have OSAs. So it is just that there is so much of prevalence of these things happening. So there will be there in the same person and plus the shared risk factors. We have heard so much of pathophysiological issues which are linking up these. So we do have hypertension, we have insulin resistance. We have coronary artery diseases, We have this complex arrhythmias which are raised three to almost two to three folds and we have atrial fibrillation is known almost to enhance 4 fold in patient with OSA. The calcitrant arrhythmias which are not really responsive to management unless OSA is triggered. This is all emerging evidence and each one of them is linked to the occurrence of the stroke all of them can cause strokes. So we have shared risk factors.

BRAIN SCAN IN OSA PATIENTS:

Apart from this we also have some evidence on imaging so you take an MRI scan and you look at white matter changes now they have not had overt clinical strokes but the covert ischemia which is going on in the brain. They do have look areas which are called as white matter change which are around the ventricle & they are graded by Taccia's grading system and anything which is graded above two and three have been linked with a little bit of cognitive decline as well as vasculocognitive what we call as VCI [vasculo cognitive impairment] beside which they have also seen they have taken patient with Alzheimer and they have taken age match controls and they have seen that patient with Alzheimer also has increased prevalence of these sleep apnea disorders. So also vascular so you do have evidence of cognitive decline and we will come to that a little later.

INDEPENDANT RISK FACTORS:

There are independent risk factors which are apart from the shared risk factors which can correlate the occurrence of these cerebrovascular incidence with OSA and that's again this is a recap again, we have talked about earlier in the forenoon we have sympathetic activation probably linking to tachy arrhythmias we have B.P.

fluctuation you know that after an apnea there is surge in heart rate and there is surge in B.P. and its happening repetitively every night. Every time the person is sleeping in the night so that's causing impaired cerebral haemodynamic hypoxemia associated enhanced inflammation and oxidative stress is again seen. Systemic inflammation due to activated nuclear factors kappa -b mediated inflammatory pathways ,there is thrombophilic situation because there is thrombosis happening. You know inflammation is linked to the production of atherosclerosis now .So there is accelerated atherosclerotic process , increase plasma fibrinogen level , increase platelet reactivity. We have also seen the enhanced right to left shunting through patent foramen ovale so these may be independently happening.

NEXT SLIDE:

And there are shared risk factors. I am not getting in to this complex diagram again. This has been projected before intensely very very complex parallel as well as things which are linked to each other which may enhance resulting in a cerebrovascular activity.

HYPERTENSION & OSA:

And then we have hypertension. This has been dealt with that why do we have hypertension associated with OSA. There have been two studies which have been quoted here. They have been dealt with before cholesterol which do say that the relative risk of hypertension in patient with severe OSA definitely is greater for the occurrence of hypertension and some evidence that

MECHANISM:

With CPAP. You can at least decrease the hypertension which is mainly uncontrolled and a lot of mechanism which have also been dealt with Dr. Goswami in his lecture in endocrine system.

APNOEA RESPONSE:

Now there are apnea responses which can have

There are these cardiac responses which have been seen decrease stroke volume, decrease heart rate ,decrease cardiac output again cardiac arrhythmias. These are repetitive that we have a whole lot of complex cardiovascular mechanism.

REM Sleep -Most Vulnerable:

We are all going hay wired when there is severe OSA & REM phase seems to be most vulnerable when this is happening because REM sleep related atonia because the tone of muscle goes down in REM .The dilator oropharyngeal muscle and the loss of respiratory drive. So whatever is happening that will be enhance in the sense the degree of and the prolongation of episodes of obstruction happens in REM sleep so there is more profound hypoxemia and therefore there is further risk happening for these events.

OSA AND STROKES:

And is there evidence as something silently happening while we sleep? Yes so when a patient does have these kind of sleep disorders with a sleep disordered breathing there could be evidence that there is transient ischemic attack happening during the night and this has been documented by the fact that one neuroimaging techniques has been able to documented by the fact that extent of white matter changes in silent ischemic episodes to happen second is by ultrasound technique. They have looked at cerebral hemodynamic flow so transcranial Doppler studies on patients who have OSAs so nocturnal studies have seen that whenever there is apnea there is decrease in cerebral blood flow through the middle cerebral artery which is documented on MCA on transcranial Doppler .Look at this happening in the person who has a severe carotid artery stenosis .You already have a compromised circulation on top of that during apnoea every time there is a further decrease .And so this is tilting the balance .So there is recurrent cerebral hypoperfusion syndrome and that is known for both vascular cognitive impairment as well as causing this silent ischemic episodes in the brain and that is like the tip of the ice burg and is a ticking bomb sometimes whenever there is a drop which is you know it dips to the point where you can have a big ischemic episode the person lands up with a wake up stroke.

STUDY:

There was a study conducted at yale medical centre there was 1000 odd of participants and again when they were all adjusted for all the confounding variables which are known to be vascular risk factors of cerebrovascular disease and they saw that patient who had an OSA...

RESULT:

Had 22 strokes on follow up the 50 deaths where as those who didn't have an OSA had two strokes...

OSAs a risk factor for stroke: Prospective cohort incidence studies:

And this is just last, in fact had already been elucidated by Prof. Vijayan very elegantly told you about these studies but these are the different studies which are population based, clinic based, and community based studies which have linked on follow up longitudinally as well as a case control or cohort studies have found that there is some kind of linkage which you cannot ignore. The occurrence of OSA and the presence of OSA in stroke as well as the occurrence of stroke in those patients who have OSA when they are followed up, so there is burgeoning literature as has been said again by Dr. Vijayan. Some of them have not been correlated. They have been negative, so there is no level one evidence to say yes –this is a risk factor but this is an imaging evidence and there certainly some way.

ACUTE STROKE AND SLEEP:

Now lets come down to what happen during an acute phase. In an acute ischemic event the 1st thing that happens is inversional sleep-wake rhythm. So we sleep in night and we are waking up in the day. So these people with strokes they are agitated during the night and they are lethargic and they sleep during the day. So the inversion of sleep-wake cycle is what happen in an acute event. In fact as a biomarker of a good stroke outcome you look for the sleep wake cycle if there have preservation of an REM sleep phase normally and you have a normal sleep wake cycle which are preserved after an acute attack, those guys do well after a stroke as compared to those that have a disrupted sleep rhythm and also the where is the stroke happening, Is it happening in the thalamus, in the mid brain in the hemisphere and how large is it? It is a small stroke, its a lacunae, its there in the internal capsule or is it a whole hemisphere which is gone, will also determine what kind of an alteration this sleep cycle you have. Now there are neuronal centre for sleep which is the pontomedullary junction, predominantly in the tegmentum, we have the pharyngeal motility which is essentially the pons is the centre for REM sleep.

Lot of sleep functions are regulated there, therefore the brain stem strokes are bad. They would have some amount of sleep disturbance. And one classic example is the lateral medullary syndrome wherein you will have sleep disorder breathing which simulate that of an obstruct sleep apnea. But then if you do have say thalamus which is involved or you have a midbrain which is involved where is the reticular activating system that is there in the midbrain. So if you have a stroke happening there, there is damage, there you don't have to implicate an obstructive sleep apnoea. As such people would to become hypersomnolent ...

THE MAJOR SLEEP DISORDERS ASSOCIATED WITH STROKE:

So this sleep disorder will be different. So the major sleep disorders associated with stroke, this is where it is enlisted they can be insomnia and also because of lot of medical conditions you have the as I said OSA's the commonest sleep disorder breathing, which happen with an acute event. We could have hypersomnia as result of central origin say for e.g. you have implication of diencephalic stroke or a mesencephalic stroke you can have because of the disrupted nocturnal sleep again medical condition because of the medication which have been given. There could be what is called as the circadian rhythm sleep disorders and a whole lot of parasomnias which includes RLS which include PLMS and most important would be REM behaviour disorders which are what is a fascinating behavioural disorders which you can encounter and it is so fascinating when you see so much can happen while you sleep. So this REM behavioural disorder is a dream in acting behaviour but they become very aggressive and this is also seen in patients in acute ischemic stroke. plus sleep related movement disorders suggests restlessness like syndrome and PLMS. Perhaps we can discuss this further in the interactive session or if the time permits.

OTHER PATTERNS OF RESPIRATORY DYSFUNCTION:

The other patterns of respiratory dysfunction include apnoeosis which is apnea during sustained inspiration. There could be non obstructive apneas mixed apnea, and there is something called Ondine's curse –the person forgets to breath when he sleep and this is not Greek mythology that actually happen. Very recently we had a patient in the ward on a 3rd stroke he actually would be ventilator dependent only in the night because while he is awake he is okay. The moment he sleeps he is saturation limit is 60 to 65% and we had to actually give him a respiratory stimulant to get him off the ventilator. This is Ondine's curse. And of course you have in huge hemispheric infarction- there could be decreased REM sleep and student of physiology you would know the cheyne stokes breathing when you have huge hemispheric infarcts there would be cheyne stokes respiration this is a whole lot of respiratory disorders or breathing disorders which you can encounter in clinical practice. So

someone who is apneustic and then develops cheyne stokes-that patient is actually improving because he is going from the brainstem nerve to the hemisphere. But some who has been breathing normally and next day you find that he has developed cheyne stokes breathing, that means there is something wrong. He is actually deteriorating .So it would prognosticate to what is happening to this patient.

OSA IN ACUTE STROKE:

In acute stroke as I said before extremely prevalent and it is seen that it is more common in men with an acute stroke as compared to women and also when there are multiple strokes as compared to single stroke. And it depends on the extent of stroke, there is some literature which said that cardio embolic may have fewer incidences but I think that it is more of a statistical mimic we need more information to comment on that...

HOW DOES THE PRESENCE OF OSA AFFECT STROKE RECOVERY?

And does it actually also implicate the stroke prognosis? What about the outcome of the patient or a stroke patient who has these sleep problems? They have reduced motivation. There is decreased cognition so they don't understand that they have to rehabilitate, they have to do these exercise programmes you need compliance and they continue to sleep. They don't give into exercise programmes obviously they are not going to do well and most important is we talked about, the cerebral hypoperfusion. So if you have an OSA or you have any sleep disorder problem then and there is decrease perfusion to the brain further on an ischemic events-now whatever is critically perfused jeopardised cerebral tissue of what we call as ischemic penumbra will become infarcted. So dying brain will become dead because there is further decrease in perfusion .That's a risk plus also increase chance of the recurrence of an ischemic event

OSA AS A PREDICTOR OF POOR OUTCOME AFTER STROKE:

Therefore OSA is a predictor of poor outcome after stroke because there is increase dependency, increased mortality, impaired cognition and concentration.

MECHANISM:

And these are the known mechanism as to why it is also a parameter for stroke outcome.

DIAGNOSIS OF OSA AFTER STROKE:

Diagnosis, we have already talked about the various mechanisms but in a stroke , patient is going to be a lot of logistic issues has to conduct a PSG because that is critical care thing and you have so many gadgets already there and they have to be compliant to have that even the PSG done just like ain children it's going to be a herculean task to get a polysomnogram in a patient with an acute stroke . So most of the studies have been done when they have established they have also used portable devices there is a SATS trial which have used that so again we don't have the level one evidence to say that we can use it....

TREATMENT OF OSA AFTER STROKE :

But there is a increasing literature which is coming on it. So the treatment of OSA after a stroke again with CPAP and it is said that it will help in whole lot of morbidity issues associated with it.

EVIDENCE:

And there is some evidence that a preliminary – the randomised control trial of CPAP and acute ischemic strokes did improve in the strokes scale that is activities and also helped in depression in motor recovery and sleepiness.

LIMITATIONS:

But then there are limitations, we have no clear guidelines as when do we do these even the studies and when do we institute the management in the form of CPAP and of course as I said we have problems with compliance....

LIFESTYLE CHANGES:

Lifestyle changes the CPAP bio levels I am not going into that there has been one study-there was a study where they did the CPAP management and seen that this a follow up those patient who has severe.(I can't

see much from here) the apnea-hypoapnea index which was severe and those patients who had CPAP and those who couldn't tolerate CPAP and if we see those who couldn't tolerate CPAP rapidly deteriorated compared to those who could tolerate and they were comparable to those who had a very mild or no OSA.

USE OF CPAP AND STROKE RISK:

Successful treatment with lower blood pressure, improve blood flow, therefore probably will reduce mortality specially after stroke

THE MAJOR SLEEP DISORDER ASSOCIATED WITH STROKE:

And again coming back to the same slide there have been further management issues besides OSA. People have tried parasomnia such as REM associated disorders with benzodiazepines like clonazepam and sleep related movement disorder like RLS and PLMS now these are not just related to sleep per say ,they may occur as parasomnias and we may discuss them further if we have time .This is a very interesting sleep phenomenon and you would be amazed how common this is!

Restless leg syndrome

Is especially - now you have this feeling of something which is –there is feeling that you should move the legs and you have these –do you know the old parents and grand parents who would have this “Pair Dabao” you know when they in sleep that actually is RLS ! essentially it is a feeling that you have to move this restlessness it isn't that there is pain essentially it's an abnormal sensation which keeps you awake and this has been correlated with a whole lot ,serum ferritin ,anaemia and so on and so forth. But there is increasing evidence that this is extremely common and it can also impaired sleep and whatever impairs sleep that's going to have problem in your quality of life subsequently similarly PLMS and as I said we can discuss if we have time further.

CONCLUSION:

So the conclusion therefore is that sleep apnea is a risk factor for stroke. As probably the evidence is going stronger and the prevalence amongst stroke survivors is particularly high. It's unappreciated stuff but how aggressive is to pursue in an acute ischemic stroke , the presence of OSA , when do we start the investigative process. Is the evidence is being gathered and all the current studies do implicate that you must treat the patient with CPAP. We need further literature to actually tell us when and how to feed them.

Thank you!!

EPILEPSY AND SLEEP

Dr K Radhakrishnan

Thank you for giving me this opportunity to talk to you.
Since I recently retired from Shree chitra, and I will be showing ...

SLEEP IN EPILEPSY

Some other videos and data from my previous institute. Let me first of all acknowledge that, these videos are actually taken from the Madavan Nair Center of Comprehensive Epilepsy Care, which I was heading recently.

PATIENT 1

I thought the best way to possibly introduce the subject would be to show you some illustrative cases, which I have come across during the last nearly 10 years. And the four that is, one is that this kind of illustrative cases can probably teach you much more than what 10 slides could convey to you. And second reason is that some of these videos are quite dramatic so that, in the post-lunch session, if somebody is tending to sleep you may be waken up by means of the dramaticity of the videos.

The first case is a 5 year old girl , who was brought by her parents with the complains of frequent awakening from sleep. They told that she has got the whole night sleep disturbed. Not only that she is disturbed by herself, she disturbs the mother's sleep also. And possibly because of that, she has got daytime sleepiness and poor performance at the school. Otherwise she was a child with a normal birth and development. She already carried an MRI which was done outside. These days, you, the first thing you do is a MRI before examining the patient. May be because of that, she already had an MRI, which was reported to be normal and we reviewed it was normal. Now I will show you the, the some of the, two events which we have recorded (video). The face is covered because of, to keep the confidentiality of the patient .she just wakes up and is restless looking here and there, and then goes back to sleep .nothing more dramatic is happening.

One more event (EEG-video-EEG-video-EEG)

Ok, that's also again almost the same ,that she wakes up and seems to be transiently confused, which last for few seconds and goes back to sleep. This happens several times during the night. So initially we thought that she may be having some dreams, or may be periodic awakening due to WHATEVER other reason is.

But during the video EEG monitoring, and those of you who are not familiar with the EEG, what it shows is a rhythmic activity, coming over the left temporal region and this is a kind of FOETAL activity, which is synchronized with this awakening episodes. And some of those were also associated with these kinds of rhythmic spikes, what we call as the MULTIPLES of spikes, which are happening over the fronto-temporal region. So here what we have demonstrated is a periodic awakening due to epileptic attacks. This is what we call the epileptic arousals, which are occurring in this child and she was treated with benzodiazepines as a single dose at bedtime which actually produce a dramatic improvement in your cognitive performance, COLLASTIC performance in the school and this episodes also stops subsequently.
(EEG changed)

(Slide: PATIENT 2)

The second patient is a 35 year old female. She has almost got daily nocturnal stereotyped events since the age of 10 years. These events, which I'm going to show you, but they were history wise characterized by vocalization, abrupt onset, along with posturing of one upper limb with the occasional urinary inconsistence associated with it. During the last 25 years, she never had a, any daytime attacks when she was awake. Always it happened during sleep. She has been treated with multiple anti-epileptic drugs without any response the REFERRAL diagnosis was EXCLUDED non epileptic events for which she underwent a video EEG monitoring at the Madavan Nair center.

This is one of her event, which is recorded.

As you can see that, this is abrupt in onset, associated with howling, and there is an asymmetric posturing, of the right upper limb. It is more DISTONICALLY POSTED and she quickly recovers, and the nurse is trying to ask her name TILL she responds. The total episode lasted for

.....less than one minute may be about 30-40 seconds.

(EEG)

This is her EEG during the episode as expected, because of the motor movements, it is largely obscured.

(EEG change)

But interictally these are, those who are not again familiar with the EEG, these are the spikes, which are the markers of epilepsy. And they were coming from the left frontal region

SYMPTOMATIC LOCALISATION – RELATED EPILEPSY

And her MRI showed this lesion which is located over the left frontal region. This what you call a focal cortical dysplasia. So she has got a symptomatic localization –related epilepsy with a left frontal cortical dysplasia which was occurring exclusively during sleep for 20-25 years. Because of that reason, this diagnosis was missed

(slide: PATIENT 3)

And the third patient is a 49 year old male, who has got a history of multiple episodes of fibrile seizures during very early childhood. But the recurrent nocturnal events started from the age of 35 years .the semiology is characterized by an abrupt loud vocalization, restlessness, and during which , he might hit other person nearby , usually his wife. Frequency of episodes are about 3-4 per night and never had any daytime episodes and no response to different anti-epileptic drugs. The MRI was normal. Here the differential diagnosis would be between a parasomnias and nocturnal frontal lobe epilepsy, with this kind of presentation, that's what clinically we should be suspecting.

I'll just show you the two of the recorded episodes

The second one is, perhaps more dramatic.

He immediately regained consciousness and could talk to the nurse.

(EEG)

And this patients EEG if we carefully see that, are characterized by these tiny spikes which are occurring over left frontal region. This is interictally inbetween the attacks

(Red squares on EEG)

And during the ictas or during the activity, this become more frequent .

(EEG change: ictal onset seizure 3)

And just to preceding this episode which is obscured by the myogenic artefact you can see those rhythmic ictal activity, which is building up over the left frontal region.

(red squares on EEG)

This patient's MRI was normal ,

(yellow squares)

.....so this is an example of what you call nocturnal frontal lobe epilepsy which again has to be distinguished from parasomnias.

(HISTORY-SLEEP AND EPILEPSY)

So, the relationship between sleep and epilepsy has been known since antiquity. and the suspicion was established by the discovery of the electroencephalogram during the 1920's by Hans BUERGER'S where you could find a co-relation between whatever is happening initially by history and subsequently by the video EEG which I showed you , and co-relating it with the electro encephalographic activity during the episodes . That means synchronized recording of the video and EEG is definitely the ultimate proof that these are either related to epilepsy or not related to epilepsy.

(SLEEP AND EPILEPSY)

So the interrelationship between sleep and epilepsy is bidirectional. That means sleep can influence epilepsy which I am going to show you by various ways. And similarly, epilepsy can also influence the sleep. Let us see how this, not always

(SLEEP AND EPILEPSY: EFFECT OF SLEEP ON EPILEPSY)

.....this can occur.

It has been well known that both sleep as well as sleep deprivations can potentiate or activate the interictal epileptiform abnormalities in the EEG and similarly epileptic seizures can also occur more frequently during sleep. There are few epileptic syndromes in which seizures occur almost exclusively only during sleep. And there are also various sleep disorders which can influence the SLEEP which we will examine. And similarly the anti epileptic medications, some of them are sedative, can also influence the sleep. And as we have shown in the last case, the diagnosis between parasomnias and the seizures are important to establish in order to manage these patients, in those patients presenting exclusively with events only during sleep.

EFFECT OF SLEEP STAGE ON EPILEPTOGENESIS

Now there is a difference between what can happen to the both, the interictal and ictal activity between the Non-REM and REM. Doctor Mohan Kumar has showed you the physiological aspect of the REM and non-REM sleep. By enlarge; the non-REM sleep is a potentiator or activator of various things which are happening in epilepsy. By contrast the REM sleep is an inhibitor. Because of that reason, there is a synchronization of the EEG during Non-REM sleep while they get desynchronized during the REM sleep. The interictal epileptiform abnormalities become more frequent or become more generalized during the non-REM sleep, while they become less frequent and more localized in, during the REM sleep. And there is also increase likelihood of seizures getting potentiated during the non-REM sleep while it is the other way around in REM sleep. Infact the REM sleep the epileptic activity, the seizure occur much less frequently then during the daytime.

EFFECT OF SLEEP ON EPILEPSY - interictal epileptiform abnormalities in EEG

Now there are few epileptiform syndromes in which the influence on sleep is much more marked. For example the benign epilepsy with centro-temporal spikes, or is also called benign Rolandic epilepsy , or Landau-Kleffner syndrome and this epilepsy with continuous spike wave activity during sleep. Here the interictal epileptiform abnormalities get preferentially markedly activated during sleep. The moral of the story is that in this kind's of syndrome if they are suspected, it's important to get an EEG during sleep also, because awake EEG may not provide you with all the information which are necessary. In temporal lobe epilepsy, again, the interictal epileptiform abnormalities get more activated during the deeper stages of the non-REM sleep while the seizures are occurring more frequently during the LIGHTER stages that mean non-REM stage 1 and 2. Why this difference between interictal and ictal is uncertain, but it may be largely related to the synchronization of the EEG activity which is happening in a different way, during different stages of the non-REM sleep

EPILEPTIC SEIZURES

There are few seizures which almost occur exclusively during sleep. One of them, as the name suggests is, nocturnal frontal lobe epilepsy, a sporadic form of it you saw in the third video. But it is more often familial and this is what it calls autosomal dominant nocturnal frontal lobe epilepsy. This is one of the epilepsy syndrome which has been clearly established to have a genetic background. Here it is related to a mutation of the acetylcholine receptor at chromosome 20 in majority of patients or there are certain other mutations which are also documented similarly almost 90% of the children with benign Rolandic epilepsy, the seizures are largely confined to sleep and they seldom get daytime seizures.

EFFECTS OF NOCTURNAL GTCS

Now the other way around, the effect of epilepsy on sleep is also equally dramatic. The repeated episodes of seizures, whether they are partial, complex partial, or generalized happening during night, as you can understand, can disrupt he nocturnal sleep. And similarly even the seizures need not occur; either the electrographic seizures or the interictal epileptiform abnormalities, there are a lot of studies available. We show that they can also disturb the sleep architecture and can produce poor sleep and because of these reasons, many of the patients....

SLEEP COMPLIANTS IN PERSON WITH SLEEP DISORDER

.....will have what you call excessive daytime sleepiness or SOMNLENCE, which may be one of the major symptoms in patients with epilepsy. And few of them, because of that, these repeated episodes can have insomnia and nocturnal spells; also will have to be differentially diagnosed.

EXCESSIVE DAYTIME SLEEPINESS IN PERSONS WITH EPILEPSY

Now, it has been shown by the Apworth sleep scale that nearly one-third of the patients, 30-50% of

patients, persons with epilepsy would have daytime sleepiness. And this could be multi-factorial, this may be related to the seizures occurring during night or interictal epileptiform abnormalities or an effect of sedative, anti epileptic drugs, or may be due to the associated primary sleep disorders which can occur concurrently with epilepsy. We will see that this is more prone to develop these associated sleep disorders because of various reasons which we will examine soon. In correction of sleep disorders in these patients has been NO sleep deprivation, is one of the ways in which seizures can occur more frequently. So, by correcting the sleep problems in these patients can also improve the sleep control. So if you get a patient with poorly controlled epilepsy, in spite of the anti epileptic medication, do not forget to ask about the nocturnal sleep because unless you take care of that, pumping in more anti epileptic drug may not have any influence on the seizure control and they may be diagnosed as having refractory epilepsy, but in fact, they are pseudo-refractory because they are not being properly managed.

SLEEP DISORDERS AND EPILEPSY

NOW, the sleep disorders, the breathing disorders ESPECIALLY the obstructive sleep apnea occur more frequently in patients with epilepsy. As you know, one of the major side effects of valproate is weight gain. Almost 30-50% of them can have weight gain related to valproate that can worsen or by itself can precipitate sleep apnea. And similarly, in patient with an obstructive sleep apnea, sedative medication like benzodiazepines and phenobarbitol can have detrimental effects. Vagus nerve stimulation, for benefits of knowledge of especially students, is a new form of treatment of refractory epilepsy which is not controlled by the medication, by stimulating the vagus nerve through a pacemaker device. And this can, again, produce breathing disorders, and in a patient with sleep apnea, it can sometime aggravate these sleep apnea, you should be remembered. And restless leg syndrome, which was briefly discussed by Dr. Padma, can be worsened by some of the anti epileptic medication like phenytoin, or zonisamide. but other drugs like GABAPENTIN, Valproate and benzodiazepine can have beneficial effects on the restless leg syndromes

AEDS AND SLEEP

Let's examine what would be the influence of anti epileptic drugs on sleep? Generally, the effect is beneficial, this may be related to the control of seizures or may be related to the suppression of the or interictal epileptiform abnormalities. They, the anti epileptic drugs, in general also prolong the non-REM stage of sleep and decrease the REM sleep. And the sudden withdrawal of it can also produce a REM rebound. And out of the drugs, valproate is more beneficial, and phenytoin IS AN older generation of drugs, is the least beneficial. But some of the anti epileptic drugs like felbomate, lamotrigine and zonisamide can also produce insomnia, sometime quite severe and this has to be inquired and these drugs may have to be changed in those patients with marked sleep disruption

AN ALGORITHM FOR EVALUATION OF NOCURTNAL SPELLS

Now with this background, now let's try to construct an algorithm in a patient presenting with the periodic events during sleep, how to approach these patients? As you know that the only way to establish the diagnosis by means of a nocturnal polysomnography . But in a developing country like ours, the facilities are very few; also it's a quite expensive proposition. So it's better to select these patients for polysomnography that IN HOME clinically you can make a diagnosis and you would require a polysomnography in order to establish the diagnosis. So, when a patient is presenting to you with nocturnal spells predominantly is be careful history taking will say that, whether there are any associated daytime events or no daytime events.

YELLOW SQUARES ON CHARTS

In those patients in whom the daytime events are present, in addition to the nocturnal events, the first investigation of choice would be to do a routine awake and sleep EEG. If that shows or interictal epileptiform abnormalities, then the patient should be managed as epilepsy and if there is no response, then you undertake a video EEG monitoring. If there is no or interictal epileptiform abnormalities, then the monitoring a long term EEG monitoring would be required.

SQUARE CHANGE

Suppose if the daytime events are absent and the events are exclusively during sleep, then you will have to clinically decide whether they are more likely epileptic or more likely to be parasomnias. How you do that will be shown in the next slides but if you feel that, it's more likely to be epileptic seizure, then you undertake an awake and sleep EEG. And if the or interictal epileptiform abnormalities are present, manage as epilepsy, otherwise you HAVE to do a video EEG monitoring. And if you think that

FRONTAL LOBE EPILEPSY AND PARASOMNIA FLEP SCALE

.....clinically there is some useful points to distinguish between frontal lobe epilepsy and parasomnias because frontal lobe epilepsy is the one which more frequently presents with, purely nocturnal events. The age usually, if it's relatively young age, and the duration is short like less than 2 minutes and the occurrence usually within half an hour to 1 hour going to sleep, and if there is a predominant dystonic posturing as you saw in the second patient and perhaps the most important clue is, if all the events are stereotyped. Even this is more in favour of an epileptic seizure and if there is a rapid regaining of the consciousness WHICH THEY LOST IT recall, that is more likely to be epilepsy. On the other hand, in most of the parasomnias, patient tends to become confused for several minutes after even the episodes are also over.

AN ALGORITHM FOR EVALUATION OF NOCURTNAL SPELLS (Three column yellow box)

So that if there are, the daytime events are absent, it's more likely to be parasomnia, then the patient will have to be monitored in a sleep centre along with video EEG and a polysomnography, combined procedure will have to be done in order to distinguish between the parasomnias and whether there is any possibility of epileptic seizure, still because patients with, sometimes with frontal lobe epilepsy may not have any interictal epileptiform abnormalities and because of myogenic artefacts, ictal activity will be difficult to record

CONCLUSION

So, let me give you some take home messages. The interaction between sleep and epilepsy is bidirectional and it can be from simple to highly complex. The sleep is an activator of general of interictal epileptiform abnormalities as well as epileptic seizures. The routine EEG in persons with suspected seizure disorder should always include a sleep recording. Awake recording alone may not establish a diagnosis. Sleep, sleep disruption due to various reasons can disturb the seizure control.

Conclusion

Epileptic discharges can alter the sleep regulation and can provoke sleep disruption and, the obvious nocturnal epileptic event need not occur to do that. Excessive daytime sleepiness and insomnias in person with epilepsy may not be always related to epilepsy, but may indicate an underlying sleep disorder for which consultation may have to be sort

Differential diagnosis between nocturnal seizures and parasomnias often need a close interaction between a neurologist which is interested in epilepsy as well as sleep specialist.

Thank you very much for your attention.

Causes of Hypersomnia Narcolepsy

Dr. MV Padma Srivastava

Sleep deprivation and Obstructive sleep apnea are the commonest causes of being sleepy in the day that is Hyper-somnolence. And of course there are whole lot of other conditions, you know, taking sedative drugs, some systemic disorders, metabolic syndromes, endocrine syndromes – the whole lot of issue is why one feels sleepy in the day. But if you look at a primary central nervous system disorder which is affecting the neural control of the sleep-wake cycle and producing a dissociated sleep-wake state, then that is Narcolepsy. So we're talking about primarily the primary CNS disorder, which is affecting... the neural control of sleep-wake cycle and that is Narcolepsy which is the primary cause of hyper-somnolence which is....

Wakefulness/Sleep: Neurophysiology

...the neural control of sleep-wake cycle and that is Narcolepsy which is...

Narcolepsy Introduction

...the primary cause of hypersomnolence, the prototypic disorder causing hypersomnolence which is a primary CNS disorder.

Now this is just an introductory slide which is sort of synopsis that this cause day time sleepiness. There are whole lot of clinical cardinal features which we will be describing and there are certain pathophysiological mechanisms where we have advanced our understanding and we are looking at a neurotransmitter dysfunction, problem in its sensitivity, may be some kind of abnormal modulation of the immune system and whole lot of genetic barring in the disorder.

Narcolepsy

And it isn't all that uncommon it is seen in 0.9% prevalence and a definitive genetic predisposition because it is seen that certain HLA haplotypes, I'll come to that in when we talk of genetic predisposition but there are some very common HLA haplotypes, HLA DR 15 and DQ 6 which in general is seen in just 30% of the population is seen invariably in these patients with narcolepsy. And if you take siblings of patients with narcolepsy, they have a 60 fold elevated risk of developing narcolepsy at some point of time and the spectrum of age where it can happen or discovered is huge – something like childhood to 72 years of age but predominantly in young age so the first peak is happening in the teens and the second peak in somewhere in early 30s and a little male preponderance.

Milestones in Clinical and Basic Research in Narcolepsy

There have been certain milestones in the research and it is as I said the last one is the discovery of hypocretin or orexin but it is evolved over a period of so many years.

Signs and symptoms

The cardinal signs and symptoms of this disorder, narcolepsy – the first is excessive day time somnolence that is feeling sleepy in the day, cataplexy, hypnagogic hallucination sleep paralysis.

Narcolepsy – Symptom Prevalence (Upper range)

Now the excessive day time somnolence, cataplexy they are all seen but if you see that EDS or excessive daytime somnolence is universal, it has to be there in a patient with narcolepsy, whereas others are seen in lesser percentage just so you can a person without the others and just have EDS as well.

Sleep Disorder Frequently found Concomitant with Narcolepsy

And the other sleep disorder which are frequently found concomitant with this syndrome are OSA, the periodic limb movement syndrome which is sleep-related movement disorders, REM behavior disorder which is a parasomnia and fragmented sleep.

EDS

Now what is excessive daytime somnolence? Now this is unwanted, unanticipated and irrepressible sleep into loops which will be just for few minutes or few seconds, so jhapki lag jathai, so there is and this

happens when there is decreased environmental stimulation; say for example now you are sitting in a meeting, you are bored, stiff therefore you fall asleep. So whenever there is decreased environmental stimulation which can be in the form of a long drive, there could be as reading a very boring book or looking at the television or a conversation that is totally unstimulating, you fall asleep. This can be natural but when this happens very frequently and sometimes it is extremely dangerous for example when you are driving it would lead to accidents. So at that period of time if the person just stops and takes a catnap for even 10 minutes or half an hour, it is very refreshing but it is transient because these interludes keep happening so in total there is a whole lot of somnolence, so what happens? There is decreased concentration and when we ask questions you don't know what to ask because you have not paid any attention because you were feeling sleepy. So there is decreased attention, there is decreased concentration so there is an apparent decreased cognition which is apparent which is not because you don't have any problem in... you have any problem in memory is because you haven't paid attention. So therefore there is a problem in performance, the performance scale goes down in school children and in students and there is an impairment which is happening in both professional as well as personal fields. So there is a problem in quality of daily living. So this is what happens with excessive daytime somnolence.

Common causes of EDS

So again there are the common causes of why one feels sleepy is not narcolepsy, it could be a chronic behavioral problems because most of the youngsters now are all owls. You know we are actually we are either owls or we are, what are called those things, larks, yes. The Larks are the ones which are early to rise and early to bed. The owls are they are awake in the day and they sleep in the... they are awake in the night and sleep in the day. So this chronic behavioral thing, you sleep through the day and then you study through the night and of course sedative mechanisms, their medications, obstructive sleep apnea, the mood disorders and the depression but when you're talking of a primary.....

Cataplexy

CNS disorder, we talk of narcolepsy. Now cataplexy is seen in 65-70% of patients with this syndrome of narcolepsy. Now what exactly is this... this is a sudden loss of muscle tone which happens whenever there is a very severe and sudden emotion – it could be anger, it could be laughter, it could be excitement, it could be anything which is..which is a surprise. So it is sudden, it is severe emotion, there is decrease in muscle tone, so some..someone who is exposed to this emotion they'll be very angry and then they lose their muscle tone, so it is generalized, they just flop down and if it is focal, it may not be generalized all the time. So if there is focal there could be slurring of pitch, speech or there could be a little facial sagging, there could be a drop of thing from a hand. So it would resemble something like a focal seizure or it could be like focal transient ischemic events which do form a differential of this focal cataplectic syndrome. So they are triggered by emotions and in these there are the respiratory movements, the extra ocular movements and there is no loss of consciousness, so these are all preserved. So there's a loss....

Sleep Paralysis

... of muscle tone. So, there are about 30% of individuals who will not have cataplexy, narcolepsy syndromes. Sleep paralysis is seen in about 60%. Now this happens when a patient is sleeping and it can happen when he wakes up and he just can't move. So his conscious, his ocular movements are ok, he is breathing normally but can't just move, it is terrifying and usually it happens once they wake up from an REM phase or when they have a hallucination or they have these dreams sequences, so they remember them and they get they wake up and they can't move. So its very terrifying, it's a dreadful experience. So the cardinal features are that the patient is unable to move on awakening. Its less commonly unable to move on falling asleep, usually there is hallucination, the respiratory extra ocular movements are spared and paralysis occur less frequently when he is in an uncomfortable position and it gets relieved whenever you give them any sort of stimuli – you call out to them or you touch them, then this paralysis gets relieved.

Hallucination

Hallucinations are seen in 15% to 50% of the cases. Hypnagogic is as they are falling asleep and Hypnopompic as when they are awakening. And there also very vivid, very frightening, very these usually, I don't know why those dreams are never really nice, they always seem to be dreadful and they may be accompanied by paralysis.

Other Common Features

And the other common features are their tendency to take short, refreshing naps during the day, trouble sleeping at night and nocturnal compulsive behavior and obesity, these could be there as associated features in

patients with narcolepsy.

Features of Narcolepsy in children

Now they, when they happen in children, they are restless and there is increased motor activity, obviously inattentiveness so there is academic, the grades fall, wide range of motor disturbances at onset, hypotonia or it could be hypertonia and motor disturbance would be a its it has to be resolved...

Narcolepsy: Burden of Disease

...It's a problem in these individuals. The burden of disease, Dr. Dutt also covered about that. Essentially that is loss of performance in your professional sphere, in your personal sphere. So there is decreased performance – workplace, school, their interpersonal problems, relationships also get into a tizzy, decreased social interactions and prone to accidents, depression, anxiety because of all this and decreased self esteem says...

Burden of Narcolepsy Disease (BOND) Study

... the spectrum will broaden as the duration of these complaints increase and they are not attended to. There has been a study which looked into this and they did find that whatever we have described, has been seen in these individuals.

How to identify the patient with Narcolepsy?

Now how do you identify an individual who may have narcolepsy? Now those who do have excessive daytime somnolence where they are not taking any medication, they are not on sedatives, they don't have, they are not obese, they don't seem to have any obstructive sleep apnea, features – now you must be well aware what those medical features are and onset is happening because, as I said, the first peak is in teens, so something is happening in adolescence and is affecting their functioning.

Assessing for Narcolepsy

The assessment we've disc.. Epworth sleepiness score has already been alluded to, it is a function of a simple clinical scale of understanding of how much is a person sleepy in the day in what kind of activities, so anything over 11 is taken as a significant sleepiness score. Sleep history, sleep diary – this is very important, somebody who is sleeping at 2 in the morning, you can't get them to be, you know brighter and bushy tailed at 6 in the morning – its not possible. So the sleep diary and also the familial – I told you there is a genetic predisposition, you'll look into that and the age of onset.

Diagnosis

The DSM- 5 criteria has these as parameters which are mandatory. You have episodes of irrepressible need to sleep at least 3 times a week for at least a period of 3 months and you may have cataplexy. The hypocretin deficiency – any level in the CSF hypocretin less than 110 pg/ml is taken as a diagnostic feature and on the polysomnograph – that is a very important diagnostic, in fact, again a mandatory exercise you need before you diagnose. I'll come to that...

Subtypes

... a little later. There a certain subtypes of the DSM – 5 has also categorized narcolepsy as narcolepsy without cataplexy with hypocretin deficiency, with cataplexy and without hypocretin deficiency, the autosomal dominance cerebellar ataxia, deafness and narcolepsy, autosomal dominant narcolepsy, obesity and type 2 diabetes and narcolepsy secondary to another medical condition.

Diagnosis

So, the diagnosis will require polysomnogram with MSLT, that is Multiple Sleep Latency test. What exactly is this doing? When a person is put to sleep, he has to sleep he has to sleep very quickly, that is the sleep onset is less than 8 minutes. And as Professor Mohan Kumar so elegantly described on the first basic lecture on sleep, the first sleep is not REM, because it going from stage 1, 2, 3, 4 and then it is going to REM. Now, here we have the onset with REM phase. So, Sleep onset REMs atleast they should be 2 or more of such episodes when you conduct so many MSLTs. So, it may be happening in the first sleep latency test that you may do or you may have to repeat this couple of times to be able to get this. And you can assess the CSF hypocretin level, as I said before, it should be less than 110. And you should not find a better explanation, that is the patient is not taking a

cocktail of drugs which will also cause this excessive daytime somnolence.

Testing – Multiple Sleep Latency Testing

So, the polysomnogram, the MSLT is this, as I have explained. There could be false negative results when they are taking certain medications. So, a medication history and a sleep diary is absolutely essential. You should look at a mood disorder, someone who has a post-stress disorder or you have other sleep deprivation problems, you will need to see. That's why you may be required to do multiple MSLTs.

DSM-5 Diagnostic Criteria for Narcolepsy

So, the DSM-5 Diagnostic criteria for Narcolepsy, as I said before, this is the mandatory thing. And presence of atleast one other thing, that is either a or b, where you have evidence of other cardinal features, cataplexy, hallucinations and sleep paralysis. c) And the CSF lowhypocretin and d) PSG.

Proposed New ICSD-3 Definitions of Narcolepsy

There are some proposed newer definitions of narcolepsy, where they said that EDS for atleast 3 months and one of the following definite cataplexy and positive MSLT result, and if narcolepsy Type I is strongly suspected clinically, but MSLT criteria are not met, repeat the MSLT, and you have either this low or less than 1/3rd of normal. And in type II, without cataplexy, you have EDS for atleast 3 months, Cataplexy is absent, Positive MSLT and you will have a normal orexin level in the CSF.

Differential Diagnosis

The differential diagnosis behavioral and circadian disturbance in adolescence. Again, coming back to sleep history and keeping a sleep diary, the medication history and we have this whole lot of sleep and seizure problems which definitely need a differential, and in that PSGs will be of great help.

Pathophysiology

Pathophysiological mechanisms have been proposed, most of them, they could be genetic predisposition, as I said the neurotransmitter problems and abnormal immune modulation.

Animal Models

We do have animal models, the first of this is the Canine cataplexy model...

... this is the picture of this canine, these dogs are all in cataplexy. And these are the murine models of narcolepsy. They are all sleeping and these are all in this cataplexy...

... So they have seen that in the Canine Cataplexy model, when there is a muscarinic cholinergic stimulation, the cataplexy would enhance. And you block that cholinergic transmission, they would all improve. And they feel that the nicotinic stimulation does nothing, so there is a neurotransmitter problem there, which is a form of increased sensitivity...

... and there is some kind of dysregulation.

Neuro-anatomic sites

The neuro anatomic site for cataplexy is Pons, but there is also secondary site, which is mesocorticolimbic dopaminergic system. Why, because you do have this. And whenever there is an increased emotion, there is decreased muscle tone, and there is cataplexy. So a secondary site has also been implicated.

Abnormal Immune-modulation

And, as regards abnormal immune modulation, what they found is, this is very recent in 2010. When they had this vaccination given to Finnish and Scandinavian children for H1N1 infection, and this was a vaccine, with using a very potent AS03 adjuvant, and they found that the prevalence of narcolepsy increased by 8-12 times in that population. And they did HLA typing they found that there was HLA DQB 0602 allele association in these children, so they went postulated that probably there is also abnormal immune modulation which may be implicated as one of the hypothesis for the occurrence of narcolepsy.

REM sleep

Now there is definitely REM sleep, which is distinctly related, with a dysfunction and inappropriate

regulation. The REM sleep, the centre response, you have what are called as REM ON cells, which fire when the REM is on and then we have REM OFF cells. The REM ON cells are cholinergic, and these are noradrenergic monoaminergic and they said that maybe it is the defective monoamine dependent inhibition of REM ON cells which may result in narcolepsy.

Hypocretin

And then this is a recent discovery of hypocretinaurexin in the CSF because this is said to..... They have found that there are decrease in number of hypocretic neurons in the murine models of narcolepsy, and they feel that there is these neurons are auto excitatory and they project on to the lateral hypothalamus. And they help in maintaining the wakefulness of the...

Absence of hypocretin peptide and signal in the CSF and the Hypothalamus of Narcoleptic Patients

... the animal. So the absence of hypocretin peptide in signal is seen in CSF and hypothalamus of narcoleptic patients as well. In a narcoleptic you don't find much of these dots which are there in, in or a normal person.

Project from Lateral Hypothalamus to maintain wakefulness

Histamine

Histamine is another neurotransmitter which supposed to maintain wakefulness. It is also low in the CSF in the patients in narcolepsy. And it can be also seen in those individuals where heparin is normal, you see, I have told you narcolepsy without cataplexy, they may not have hypocretin which is low in CSF. In such individuals, histamine is still low. But histamine is not low in patients who have excessive day time somnolence because of obstructive sleep apnea. So, therefore histamine is now being taken as a biomarker to in those patients who have an EDS because of a central problem and not because of a peripheral obstruction.

CNS nuclei for wakefulness

The other CNS nuclei for maintaining wakefulness you have locus ceruleus which is giving norepinephrine. We have Raphe nucleus which is producing serotonin. we have the tubo mammillary nucleus which is producing histamine. The ventral tegmental area which is dopamine. And basal forebrain which is causing which is producing acetylcholine. In these they say that the hypocrtine neurons which are auto excitatory they're all projecting from the hypothalamus and projecting to all these nuclei and maintaining wakefulness.

Autoimmune process

And very recently they have also found there's an auto antigen tribbles homolog 2. Which probably is destroying the hypocretin producing neurons. Something like an autoimmunity and this discovery has triggered certain trails with immunoglobulin, and they have tried giving IV Ig in patients with narcolepsy. When they discovered with some resolution of excessive day time somnolence. Which was temporary, so this at the most I must say in phase 2

Genetic Factors

Now coming back to the genetic factors. There is 40% increase risk in the first degree relatives. Who have narcolepsy to develop narcolepsy. As I said before a whole lot of them carry the HLA DR15 and HLA DQ gene. Sibling have 60 fold elevated risk and it's also seen to be associated with HLA DQ of the 101 02 and DQ .well there are whole lot of HLA haplotypes which have been indentified with this syndrome. The geno wide association (GWA) studies have also seen protective variants which protects against narcolepsy and they found association between the SNP (single nucleotide polymorphism) the t-cell receptor of alpha locus and narcolepsy. And there is one geno wide association study in 202 candidate genes in 222 patients and they found the six genes. Which these numbers probably don't make much relevant to ours. It is just to drive on the point that yes they seems to be definite genetic predisposition to the syndrome

Management

And the management is both non-pharmacologic as well as pharmacologic. Sleep hygiene- you know you can't read today it how more important it can be- definitely there

Pharmacologic Treatment

And that you need to have definite- you know regular sleep schedules, and don't try to cram up everything in the last minute. Why? because sleep is not something that you can bypass or -sort of you know- that you can compromise upon. That seems to be one of those things- okay, I can stay up in the night and I can do this thing- that probably you should get above that habit. And in the pharmacological treatment, Prof. Sharma had already covered that. We have the CNS stimulants in form Methylphenidate, Modafinil, Dextroamphetamine, Methamphetamine, Amphetamine ; these are also habit producing drugs so they are not over-the-counter drugs, there are special prescriptions which are needed for these drugs. And for cataplexy you have Sodium oxybate, Tricyclic antidepressants, SSRIs and we need to be careful about these because these are again acting upon the REM sleep so they may sometimes exhibit other sleep disorders. But most commonly used are in fact R modafinil which is relative of modafinil, and they do have side-effects- they can have headaches, they can have- you know- gastrointestinal complaints, they can cause dizziness, so it is not that just to stay awake let's take these drugs and let's stay awake in the night and study, that should not be the take-home message. These are important drugs and don't play around with it.

Summary and key messages

So, summary and the key messages. Untreated excessive daytime sleepiness is dangerous to self, dangerous to others. Narcolepsy is always a consideration in the adolescent and adult with unexplained EDS so daytime sleepiness. It's a diagnosis with a common presentation and a very clear diagnostic criterion so not everybody who is falling asleep in the day is having this disorder

Summary and key messages (contd.)

...criteria. So not everybody who is falling asleep in the day is having this disorder. Over the past few decades, we have had, you know, advances in our understanding of pathophysiology – most important has been the discovery of hypocretin deficiency and we don't have pathophysiology based treatment because we don't have level 1 evidence anywhere near that with IVIG and other immune modulation. Yes, symptomatically we can benefit by non-pharmacological assessment as well as certain CNS stimulants. The etiology is still, probably still mebulous....

... Narcolepsy is a disorder of sleep-wake state and the instability appears to be related to injury or dysfunction, the hypocretin mediated signaling and spectrum of patients-related symptoms is pretty broad and you could have even patients without the other cardinal features like cataplexy, the hallucination and sleep paralysis.

Thank You.

ENDOCRINOLOGY of SLEEP

Dr. R. Goswami

I'll just focus on growth hormone and adrenal axis.

SLIDE 1: CIRCADIAN RHYTHM AND SLEEP

Now before we talk about hormonal changes, we need to know certain basics about circadian rhythm; how..... What is the genesis of circadian rhythm? What is the symptom responsible for that? It is the continuous rhythm in the body which is separate from the environmental clues and it has autorhythmicity of 24-25 hours. The nucleus for this is called suprachiasmatic nucleus which is MASTER for circadian clock. It is bilateral present to the anterior hypothalamus near third ventricle. This nucleus determines the circadian rhythm. It has autorhythmicity of around 24 hour period, but it needs entrainment and this entrainment comes from the environment.

2. ENTRAINMENT OF CIRCADIAN CLOCK

From the pupil, light enters and this stimulates the cones and rods and ganglion..... photopigment in the ganglion cell and through retino hypothalamic tract, the projection goes to the suprachiasmatic nuclei. This is one way by which the environmental clue can entrain the inherent rhythmicity in the suprachiasmatic nuclei.....Of course, beside day and night, we have body temperature, exercise, feeding which can modify this circadian rhythm to some extent but primarily, it is a light cycle.

SLIDE 3

Somehow, it regulates its autorhythmicity how ADHESIVE to body's need and behavior.....and we have a biological day and biological night. During the day time, we are alert and awake, during the night time, we are sleepy. And the same way, there are circadian rhythm in the hormones which are adhesive to this body behavior. And how it happens? The projections from suprachiasmatic nuclei. They project to the hypothalamus. They project to the cerebral cortex. They project to the pineal gland through a circuitous route. This is very circuitous compared to the other route through autonomic system and with the help of these projections, there is a balance between circadian rhythm and biological day and night.

4. MELATONIN AND THE BIOLOGICAL CLOCK

So, what you see, this is repetition of what you said. The external clue enters through the eye, goes to the suprachiasmatic nuclei; and there are projections from this nuclei to the cortex, and hypothalamus again, which regulates the hormonal rhythm; circadian rhythm with the hormone and there is another circuitous route which goes down to the thoracic vertebra- upper thoracic vertebra, and then through ganglion back to the pineal gland which makes the melatonin. So, these are, just like the autorhythmicity in the suprachiasmatic nuclei because there are projections to the pineal gland. There is a rhythmic discharge from the pineal gland also, which matches that of the suprachiasmatic nuclei.

5, GENERAL ASPECTS OF SLEEP

So you can say that by enlarge the circadian rhythm and biological day and night matches. But difference can happen and that's what we are going to discuss whether the circadian rhythm are the one which determine hormonal changes or whether the hormonal changes give rise to the differences in the biological day and night as reflected in the EEG. This part has been covered in the morning, just to show in the cartoon form. The first sleep is usually non-REM sleep which is taken as equivalent to intense sleep. Afterwards then, you have REM sleep. So first sleep is NREM sleep which has phase 2 and 3, 4, and then these phases come again, but in a shallow form, but primarily it is a REM sleep which occurs near morning.

SLEEP AND ENDOCRINOLOGY

So, there is an inherent rhythm in the hormonal system because of the projections to hypothalamus from suprachiasmatic nuclei. And you can say that whatever we have seen in the hormonal changes in the circadian form, it is the reflection of suprachiasmatic nuclei, it's not something else. But then, we can study this, that whether it is the circadian rhythm or it is the environmental induced changes in the hormones and there is a protocol called Force Protocol where we make the condition of dim light, person remains awake-we ask him to remain awake, take isocaloric food at equal INTERVAL. That's how he escapes from the environmental clues and whatever we see, that is feature of circadian rhythm..... Repeated hormonal samples are taken to see what are

the circadian pattern in the hormones.

SLEEP AND HORMONES

Various hormones are important in circadian hormone and day and night sleep and the important ones these are the two top most-growth hormone releasing hormone and growth hormone axis and corticotrophin releasing hormone and cortisol axis. These are most important hormones followed by melatonin which is required in cortisol sleep. This is probably determined by the circadian rhythm. This also by circadian rhythm but growth hormone releasing hormone and growth hormone, they are determined not only by the circadian rhythm also, but by the environmental clues also. I will come to the importance of all these in subsequent slides. Other minor hormones, various neuropeptides, ghrelin, somatostatin, sex hormones which can influence the sleep.

SLEEP AND HORMONES

So we can say, what has been known for years is that first half of sleep, we have growth hormone releasing hormone and growth hormone. In the second half of sleep near morning, we have more of corticotrophin releasing hormone and cortisol..... that's why morning cortisol is high. We have morning cortisol which is around 25ng%. There is evening which is around 5, so morning cortisol is high because it starts rising from the early morning itself; from 6 am around.

SLIDE

This is shown in this cartoon from both growth hormone and cortisol axis. So this is the beginning of sleep in the night. We see first phase as soon as the sleep begins, the growth hormone start rise happens- it remains till midnight and then falls. It has importance in the diabetes also but, I've covered that Somogyi phenomenon is related to this and Somogyi phenomenon they are related to this growth hormone surges and cortisol surges. The cortisol surge occurs from midnight and goes on in the morning because this the period of awakefulness and REM sleep. It is said that these hormones, these changes relate to sleep patterns-REM sleep and NREM sleep. NREM sleep which is also slow wave sleep or intense sleep is related to the growth hormone and growth hormone releasing hormone axis whereas the awakefulness or tendency to awakefulness or disturbed sleep; you can say that what happens in the morning is because of the cortisol-CRH axis..... Though what I told is about human being in general but there is a sexual dimorphism..... this what you see here single peak of growth hormone is typical of male but in females you see multiple peaks of growth hormone in the night....so there is not only one peak but you can see a peak here also. So this sexual dimorphism may have some relevance in the form of biological adaptation because females they are more prone to depression and disturbed sleep in later age compared to males; and this may be a bio-adaptation that they have more of a disturbed sleep so they have more of growth hormone but this is just a hypothesis.....

SLEEP AND HYPOTHALAMIC-GROWTH HORMONE AXIS

But this appears to be circadian rhythm but it may not be.... Because you see a growth hormone rise if you sleep during daytime; then also you can have some rise in growth hormoneso it means this circadian rhythm is influenced by the environmental clues also; but this is not seen in CRH-cortisol axis-that is not influenced by environmental rhythm. Now whatever changes you have seen you can say that whatever growth hormone rise you have seen in the early sleep. It could be because of the non REM sleep rather than growth hormone giving rise to non-REM sleep, it could be non-REM sleep giving rise to growth hormone surge..... You can argue like that also. But it's not like that, the infusion studies, they have shown that if you infuse growth hormone releasing hormone to volunteers, there is surge of growth hormone and induction of slow wave sleep. So, it means, it's the GHRH infusion which is giving rise to slow wave sleep or NREM sleep. It is not the other way. When you give GHRH, not only there is induction of slow wave sleep, there is decrease cortisol also, which in a way is better for sleep. So by these 2 things, you can say growth hormone surge happens in the early phase of sleep, is good for the intense sleep by 2 ways- By growth hormone itself and by suppression of cortisol in the early morning.

SEXUAL DIMORPHISM

There is little bit more about sexual dimorphism in growth hormone releasing hormone, because these are 2 main hormones which lead to the sleep and these are being utilised for the treatment of sleep disorders. So I'll focus more on these 2 hormones, and that's what the title of the today's topic. You can say that when growth hormone releasing hormone is given, they increase growth hormone and decrease in the cortisol early morning. But in the females, when you give growth hormone releasing hormone, there is increase in growth hormone but

there is increase in the cortisol also, in early morning..... So this is called Sexual Dimorphism. When you give growth hormone releasing hormone to male, there is increase in growth hormone in the early part of the night, and in the late night,..... Early morning, there is suppression of cortisol. But in the females, when you give growth hormone releasing hormone, there is rise of both growth hormone in the early part of sleep and cortisol in the morning, which is not good for the sleep point of view, because the rise in cortisol will give rise to wakefulness. So this dimorphism has to be important and this could explain why there is increased INCIDENCES of depression in females, especially after menopause..... there is more Cushing's syndrome in females. Till now, we don't have any clear cut reason why Cushing's syndrome is more common in females rather than males, but this could be the reason that growth hormone surge which happens in the early part of release instead of suppressing cortisol in the morning is just like as we have seen in males, in females, it increase cortisol in the morning. In other words, cortisol levels, they are inherently high in the early morning phase in females compared to the males.

SLEEP, GH ANALOGUE AND SOMATOSTATIN

These are just hypothesis but then for things which you don't know. But from volunteers study and from the inference studies, in the inference studies, we have come to know that, that's what happens in the females unlike males.

Ghrelin is just like growth hormone. It stimulates growth hormone. It is a hormone which is released from stomach, increases the appetite, and because it releases growth hormone. we expect that it will have effect like that of growth hormone, which will also prove that growth hormone leads to increase NREM sleep in the morning and that's what we see after ghrelin infusion in the volunteers. The infused ghrelin, which is just like growth hormone, which is growth hormone receptor secretagogues in the hypothalamus; when you give ghrelin, there is increased slow wave activity which is similar to that of growth hormone. So this tells us that growth hormone and its analogues, growth hormones and its secretagogues in the hypothalamus, they leads to increased NREM sleep in the early phase..... We expect opposite from the somatostatin and that's what have seen when you infuse somatostatin in volunteers, the slow wave activity is reduced. so this tells us that growth hormone rise in early part of the night is very important for the sound sleep and intense sleep. This is totally different what we have talked in the morning, that excess of growth hormone in acromegaly give rise to obstructive sleep apnea. But here we are talking the normal PRG, there we were talking about the abnormal supra high levels. The arginine which is somatostatin antagonist increase the slow wave sleep, so in other words, there are many evidences which says that growth hormone rise after sleep which happens once in the male and multiple times in females, is good for the NREM sleep or the intense sleep.

SLEEP AND CRH-ACTH-CORTISOL AXIS

Now let's see the second axis. The CRH..... There is rise in cortisol.....there is rise in CRH in the experimental animals if you see the CSF levels of CRH. So we have assumed that this rise in cortisol, seen in the early morning because of the CRH and it is the cortisol which determines the REM sleep. It could be CRH, but it could be cortisol also. That's what the hypothesis is going on and you see , when there is the same cortisol, is HELD against that men cortisol in the early morning before awakening, there is more of REM sleep. First you tell, so one way to sort it out is to give CRH infusion to volunteers to give cortisol infusion to volunteers, or to give ACTH infusion to the volunteers and see the effect of sleep and different phases of sleep. When pulsatile, CRH is given in young males, it is available in commercially and can be given 100 mg usually..... we routinely give to test the ACTH axis. So when, volunteers were given intravenous corticotrophin releasing hormone, the cortisol increased in the night, but the growth hormone surge bunted and there was decreased slow wave sleep, so you can see that if you give CRH, it has given the surge normally. The growth hormone surge was stopped, so what you can see that more of CRH give rise to less of NREM sleep in the early morning. And these changes which are seen with CRH infusion, they are more intense with ageing. I'll come to this point, why they are more intense with ageing after sometime, and then we see the sleep pattern of ageing, Ageing and depressed patients. They are almost similar.

SLIDE

The importance comes here of CRH. Just now, till now, I've told you to summarize that growth hormone surge in early phase of night is important for the induction of sleep and good sleep and the cortisol surge which is seen in the early morning is not good. It creates wakefulness and disturbs sleep..... multiple awakenings. In stressed rats, there are experimental studies, if we give CRH antagonists..... Its alpha helical analogue of CRH not receptor antagonists but CRH antagonists which is available in the form of astressin. The REM sleep was decreased when we give CRH, there is more of REM sleep, but if you give its antagonists, we expect REM sleep to be decreased. That's what happens in the experimental animals. Same thing can happen if you give the receptor antagonist of CRH in human volunteers. These are compounds which are in development stage. So, when the CRH receptor antagonist was given to the volunteers, there was more of NREM sleep and less of REM sleep.....

And reduce awakening after CRH receptor antagonists. So, in other words, we can say that the growth hormone in early part of night, early phase of night is good, and CRH is bad. And CRH antagonists, whether antagonists of hormone itself, or its receptor antagonists, they'll lead to better slow wave sleep. This CRH receptor antagonists are in the development phase, and this is one way to counteract sleep induces the disturbances of the sleep which are seen in patients with various sleep disorders, depression or schizophrenia.

(SLIDE)

So, these changes, whatever I told, could have been because of CRH, because ACTH ultimately will give rise to increased ACTH if you infuse CRH. But people have not seen these changes after the infusion of ACTH. They have not seen similar changes which is seen in CRH on sleep are not seen with ACTH.

(SLIDE)

But STEROIDS, remains whether the cortisol rise is determinant of the sleep changes which are seen in the early morning or it is the CRH itself. This again could be easily proven in forced protocol when we give continuous hourly infusion of hydrocortisone in physiological dose; there was increase slow wave sleep. This is unlike CRH because if you infuse CRH slow wave sleep is decreased, but if you give cortisol infusion in physiological dose, there is an increase slow wave sleep. In other words, whatever changes you saw, whatever changes you are seeing in physiology, they are seen because of CRH not because of ACTH or not because of steroids. This is about the physiology, but this doesn't remain when you give high dose steroids and reverse happens of the normal physiology. So, in normal physiology, the early cortisol rise in the morning is reflection of the CRH rise and it is the CRH which reduces the REM sleep.

SLEEP AND AGEING AND DEPRESSION

Here's the cartoon which shows what are the various changes which shows in the different individuals, young person's- more of the NREM sleep, this sleep goes down in the elderly people, person with depression has pattern like that of senior person. So what you see in a depressed person you have less of NREM sleep, which is same as that of elderly person. So sleep pattern of young depressed person is same as that of elderly person, In other words, less of NREM sleep in early phase of night. So if want to make these 2 people normal just like of the young person, what you have to do is induce hormonal changes, like that of this person. So that's how the efforts are going on to make sleep profile similar to that of young people by giving hormonal analogues. Growth hormone releasing hormone is one way, but then of course, this option is not viable because of its injectible form and cost. So we have to depend on oral analogues subsequently.

SLIDE

This is the total of all the slides on the sleep pattern and hormonal changes. This is early cortisol rise; in the depressed young person which is more than that of normal person, there is normal young person, cortisol of young person, normal young person, depressed young person, cortisol of depressed young person. You can see it's more in young person. If you see the growth hormone surge, normal growth hormone surge in young person and this is the kind of surge which is seen in depressed young person. So you see less of growth hormone surge in depressed person in the early morning compared to normal. Same thing happens for the cortisol. In both old person and normal person, there is cortisol surge but this surge is much more. So, in other words, there is antagonism between growth hormone releasing hormone and CRH. So this antagonism, you have to tackle to take care of sleep disturbances though it is easier said than done.

CLINICAL RELEVANCE: SLEEP ASSOCIATED CHANGES

Because there is no good drug available on how to use this information in these 2 hormones.

There are various disorders of sleep described due to misalignment in sleep cycle when the circadian rhythm and inputs, they get disturbed, then you have sleep disturbances. For example, a person who used to sleep during the night time goes for night shift, then these sleep disturbances happen, and hormonal changes are one way to take care of this. Obviously, we all know that melatonin has sleep promoting effect, and this can be used as a substitute to take care of the misalignment in the circadian and sleep cycle. Cushing's disease patients are often depressed. This interesting information which I can across- beta blockers, they are known to increase wakefulness, and often beta blockers are given to patients with myocardial infarction, post M.I. the opposite is good to those patients who are anxious. But if person is not anxious, if you are giving beta blockers for the sake of secondary prevention, then it could promote wakefulness by antagonizing melatonin. A new concept is coming, if you give beta blockers with melatonin, it will reduce this wakefulness.

SLIDE

There is very recent information which is coming these days, that if you do day and night shift, people are more prone to obesity. There is LARGE study in more than one lakh women and when they were asked about the presence of diabetes or obesity, it coincides with the number of hours they have worked, number of years they have worked in night shift, larger is the prevalence of obesity and diabetes mellitus. There is a biological basis

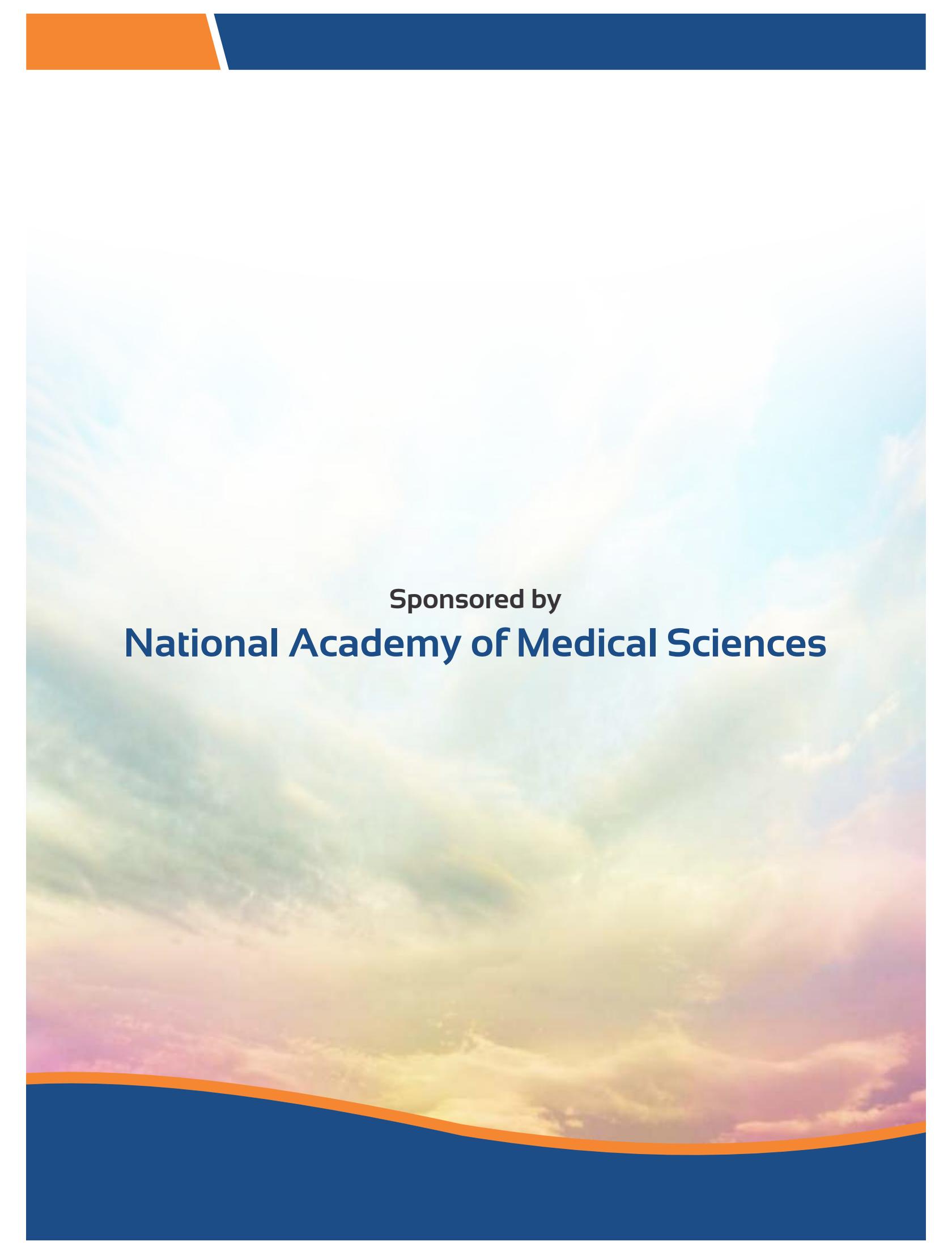
for this from the experimental studies, animals who were awakened at night; they tend to eat more- this was discussed early in the morning. They tend to become obese as they eat more during the awake period. This misalignment can give rise to infertility also, but there is limited data on this. I could find only few studies.

MOLECULES WITH POTENTIAL ROLE IN DISORDERS OF SLEEP

Beside growth hormone analogues and CRH antagonists, melatonin is the other way, simpler way to tackle this misalignment because you know, nocturnal peak of melatonin normal persons happens at 2 am and those who are depressed and those who have obstructive sleep apnea and sleep disturbances, this melatonin peak may be shifted. We don't know the reason for this because primarily, it is circadian driven melatonin rhythm. It's not by the environmental clues but of course the minor disturbances are seen in sleep disorders and this can be made use of when we treat these patients. A person is awake during day time after night shift; person who do night shift, they often have difficulty in maintaining sleep during day time. You can give them sustained release melatonin preparation to support their sleep stage.

SLIDE

Then as discussed, growth hormone releasing hormone is not a good choice for obvious reasons because it's costly, injectible, not available. CRH antagonist s, they are being tried and they are being in phase I and phase II trials.



Sponsored by
National Academy of Medical Sciences