ORIGINAL RESEARCH PAPER
Volume-6 | Issue-12 | December-2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 93.98
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

HYPERSOMNIA (DISORDERS OF EXCESSIVE SOMNOLENCE) : A REVIEW

Psychiatry

Gayathri Vijayalakshmi Assistant Professor, Dept of Psychiatry, Karuna Medical College, Palakkad ,Kerala, India

ABSTRACT

Hypersomnia is common public health problem . Several causes of excessive sleepiness range from insomnia to obstructive sleep apnea. Excessive sleepiness can be debilitating symptom.The impact on cognition, work , family and social life is significant. Serious effects like accidents put public safety under scrutiny. There are physiological and legal implications of this problem. Negative impact on socio occupational life can be prevented by treatment.

KEYWORDS

CLASSIFICATION [1]

Causes of Excessive day time sleepiness [EDS]

1. Sleep apnea syndromes
2. Narcolepsy
3. Upper airway resistance syndrome
4. Periodic limb movements in sleep
5. Insufficient sleep syndrome
6. Depression
7. Medication[sedatives, tranquilizers.anticonvulsants,antihi stam inics]
8. Acute medical illness of the mononucleosis type, respiratory and gastrointestinal infections
9. Post surgical and postanesthetic states
10. Chronic neurological illness :multiple sclerosis,dementia
11. Metabolic derangements :hypothyroidism ,Addison disease
12. Encephalitic diseases, Trypanosomiasis
13. Lesions of hypothalamus : Kleine – Levin Syndrome Hypothala mic tumor or granuloma
14. Drug dependence
15. Post traumatic hypersomnia
16. Space occupying lesions
17. Idiopathic hypersomnia

CLASSIFICATION[1]

A]NARCOLEPSY:

1.With cataplexy

Subtypes:

- hypocretin gene mutations
- with normal hypocretin level in the CFS
- multiplex/familial subtypes
- HLA DQB1*0602 negative cases
- isolated cataplexy

2.Without cataplexy

Subtypes:
- with low hypocretin-1 levels in the CSF
- with cataplexy-like or atypical episodes
- HLA DQB1*0602 negative cases

3. Due to a medical condition

Subtypes:

- secondary to Parkinson's
- disease
- Posttraumatic narcolepsy
- Genetic disorders associated with secondary narcolepsy with cataplexy
- Genetic disorders associated with narcolepsy and sleep-related breathing disorders
- secondary to brain tumors, infections or other brain lesions

B]HYPERSOMNIA
1. Recurrent Hypersomnia Subtypes Kleine –Levin Syndrome Menstrual related
2. Idiopathic hypersomnia with long sleep time
3. Idiopathic hypersomnia without long sleep time
4. Due to medical condition

Subtypes
- Secondary to parkinson's disease
- Posttraumattic hypersomnia Genetic disorder associated with primary CNS somnolence
- Genetic disorders associated with primary CNS somnolence and sleep related breathing disorders Secondary to brain tumors , infections or other CNS lesions
- Secondary to endocrine disorder
- Secondary to toxic and metabolic conditions

5. Due to drug or substance
- secondary to abuse of stimulants
- secondary to abuse of sedative- hypnotic drugs
- secondary to cessation of stimulant prescription
- secondary with prescription of sedative compounds

6. Not due to substance or know physiological condition
- associated with a major depressive episode
- as a conversion disorder or an undifferentiated somatoform disorder
- associated with seasonal affective disorder

7 Physiological hypersomnia, unspecified

Central disorders of hypersomnolence are classified as follows: [1]

1. Narcolepsy type 1
2. Narcolepsy type 2
3. Idiopathic hypersomnia
4. Klein–Levin syndrome
5. Hypersomnia due to a medical disorder6. Hypersomnia due to a medication or substance
7. Hypersomnia associated with a psychiatric disorder
8. Insufficient sleep syndrome 9. Isolated symptoms and normal variants (a) Long sleeper

EVALUATION[2]
1.History

2. Self Rating Scales Of Sleepiness

3. Sleep Wake Diary

4. Polysomnography

Agood history would differentiate complaints of fatigue & daytime sleepiness.Questionaires such as Epworth sleepiness scale or Stanford Sleepiness Scale are attempts to standardize the evaluation of self rated symptoms of sleepiness [2]

The Epworth scale measures average sleep propensity over eight common situations .[4]

The scale is simple & short . The test was developed by Johns at the EpworthHospital in Melbourne, Australia. The propensity to fall asleep is rated as 0, 1,2,3. The maximum score is 24, normal is assumed to be 10 or less. This scale correlates roughly with severity of obstructive sleep apnea & improves after CPAP treatment.[5] The Stanford Scale measures average subjective feelings of sleepiness (fogginess, beginning to lose interest in staying awake).[2,3]

History should include recording of normal bedtime, waketime, average hours of sleep . Questioning bed partners is absolutely essential in evaluating patients with EDS. A history of loud snoring& observed gasping or apnea is suggestive of obstructive sleep apnea syndrome. History of leg jerks suggests periodic limb movements in sleep. Physical examination should pay attention to upper airway(nose, mouth, throat) ,neck circumference, signs of right or left heart failure or hypothyroidism.

OSAHS:OBSTRUCTIVE SLEEP APNEA HYPOAPNEA SYNDROME

Definition:Unexplained excessive daytime sleepiness with atleast 5 obstructed breathing events (apnea or hypoapnea per hour of sleep

Epidemiology :1-4 % in middle aged males

1-2 % in middle aged females

During sleep, closure of the upper airway results in cessation of airflow despite continued respiratory effort resulting in brief apnea followed by awakening. Apnea due to upper airway collapse is defined asnearly complete cessation of airflow associated with oxygen desaturation or an arousal from sleep and hypoapnea is due to partial collapse of the upper airways.[6]

Apnea is defined as cessation or near complete cessation that is more than 90% reduction of airflow >10 seconds despite continuing ventilator effort with five or more such episodes per hour of sleep and is usually associated with a decrease of
>4% inoxyhemoglobin saturation. Hypoapnea is characterised by a reduction of >50 % in airflow for >10 seconds associated with a >3% decrease in oxygen
saturation and or arousal.[8]

Diagnostic criteria for obstructive sleep apnoea, adult (adapted from ICSD-3)[1]

(A and B) or C satisfy the criteria

A. The presence of one or more of the following: 1. The patient complains of sleepiness, non-restorative sleep, fatigue or insomnia symptoms 2. The patient wakes with breath holding, gasping or choking 3. The bed partner or other observer reports habitual snoring, breathing interruptions or both during the patient's sleep 4. The patient has been diagnosed with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation or type 2 diabetes mellitus

B. Polysomnography (PSG) or out-of-centre sleep testing (OCST) demonstrates: 1. Five or more predominantly obstructive respiratory events [obstructive and mixed apnoeas, hypopnoeas or respiratory effort-related arousals (RERAs)] per hour of sleep during a PSG or per hour of monitoring (OCST) or C. PSG or OCST demonstrates: 1. Fifteen or more predominantly obstructive respiratory events (apnoeas, hypopnoeas or RERAs) per hour of sleep during a PSG or per hour of monitoring (OCST)

Risk factors
Age, gender (male), ethnicity (black, Hispanic) ,anatomical abnorm alitiesof craniofacial region & upper airway, thick neck with circumference more than 17 inches(Male) ,16 inches (female), body weight,use of alcohol, sedatives or tranquilizers and narrowed airways due to enlarged tonsils or adenoids. [10]

OSA can cause systemic inflammation , oxidative stress, sympathetic nerve activation, endothelial dysfunction, procoagulant activity, intrathoracic pressure changes and metabolic
dysregulation .[9]

Systemic inflammation due to OSA
Increased circulating levels of CRP have been consistently reported in both adults , as well as in children with OSA and are reduced on effective treatment . Nuclear factor kappa B , an important factor for activation of inflammatory pathways has been found to be increased in OSA. Cd4 & CD8 T cells of patients with OSA undergo phenotypic & functional changes with a shift towards type 2 cytokine dominance & increased IL4 production. [8]

Oxidative stress due to OSA
Research has demonstrated that there is increase in thiobarbituric acid reactive substance(TBARS) levels in patient with severe OSA and treatment with continuous positive airway pressure reduced lipid peroxidation events. There was increased level of oxidized .Low density lipoprotein leve in OSA. Urinary 8–hydroxy -29-deoxyguanosine excretion was significantly higher in patients with severe OSA whichsuggests oxidative damage in OSA. [11]

SYMPATHETIC NERVE ACTIVATION
Increased sympathetic nerve activity has been reported in OSA due to activation of peripheral chemoreceptos by hypoxia, hypercapnia and apneas leading to peripheral vasoconstriction , increase in blood pressure. Elevated levels of norepinephrine in plasma , increased concentrations of catecholamines in urine were also seen in patients with OSA.Chronic sympathetic activation important factor for development of cardiovascular disease . [11]

ENDOTHELIAL DYSFUNCTION
Endothelial dysfunction is a risk factor for cardiac abnormalities . Endothelial dysfunction results in increased vasoconstriction and reduced vasodilation[12]

PROCOAGULANT ACTIVITY
Elevated levels of plasma fibrinogen, exaggerated platelet activity & reduced fibrinolytic activity suggesting a hypercoagulable state in OSA. Increase in mean platelet volume has been found in a majority of patients . With CPAP treatment exaggerated platelet activity and increase in mean platelet volume has been reduced [12]

INTRATHORACIC PRESSURE CHANGES
In OSA the repetitive inspiratory efforts against a closed upper airway leads to increased negative intrathoracic pressure, resulting in increase in transmural gradients across the atria , ventricles and aorta.An increase in aortic transmural pressure can cause aortic dissection in OSA patients.[12,15]

METABOLIC DYSREGULATION
OSA is independently associated with metabolic syndrome . Features associated with metabolic syndrome are proinflammatory state,prothromboticstate,hyperleptinemia,h ypoadiponectinemia, hyperuricemia, endothelial dysfunction and microalbumininuria.[16]

DIAGNOSIS
ASSESSMENT: based on symptoms, laboratory investigations (Polysomnography)

Symptoms
Snoring, choking attacks terminating with a snore and witnessed apneas by bed partner. Non restorative sleep, nocturnal restlessness, vivid dreams, gastroesophageal reflux, insomnia with frequent awakenings , nocturiahypersalivation and diaphoresis[13]

patients.[37]

The optimal CPAP level should not only prevent sleep disordered breathing , but allow for maintenance of high quality, hypoapneas.

Adherence of PAP is only 40-60%. Methods to enhance Adherence Education of treatment to the patient & bed partner Careful mask fitting , testing for leaks Routine use of humidification Treatment of nasal congestion Careful mask fitting Early interventions for side effects Regular follow up visits with the physician

BIPAP THERAPY

BiPAP allows independent adjustment of the pressures delivered during inspiration & expiration compared to CPAP delivers constant pressure during both inspiration and expiration. Bi PAP therapy is prescribed in patients with OSA who cannot tolerate high CPAP pressure or have complications following CPAP therapy .

ORALAPPLIANCES

Oral appliances [Mandibular repositioners, tongue retaining devices and palatal lifting devices] are indicated for mild to moderate OSA who prefer OA to CPAP therapy or in whom CPAP therapy has failed. Complications of oral appliances include excessive salivation, dental misalignment with bite changes , tempero-mandibular joint disease, gum irritation, salivation,tongue pain. Contraindications to the use of oral appliances are less number of teeth, patient is unable to protrude mandible forward and open jaw widely, pre-existing temero mandibular joint problems, severe bruxism and those with full dentures.

CHILDHOOD OSA

Obstructive sleep apnea is a common condition in childhood and can result in severe complications if left untreated.[23] A significant association with obesity has been observed, however some children with enlarged tonsils and or adenoids may be even underweight.[24] The patient usually presents with snoring and other respiratory problems like mouth breathing , choking, gasping episodes in the night.[25] Poor school performance and neurocognitive deficits has been reported. [26,30].For definitive diagnosis an overnight polysomnographic evaluation is the gold standard. The specific treatment ranges from simple lifestyle modifications to surgeries like adenototonillectomy. [27,28,29]

UPPER AIRWAY RESISTANCE SYNDROME

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

PICKWICKIAN SYNDROME

This entity consists of obesity, sleep disordered breathing , hypoxia and chronic hypercapnea during wakefulness in the absence of other known cases of hypercapnea.

NARCOLEPSY

Narcolepsy is an example of dissociated sleep wake phenomenon in which (Rapid Eye Movement) REM sleep appears in wakefulness.[43] Prevalence is about 0.08 %. Majority of the cases (90 %)with narcolepsy carry the HLADR15 & HLADQ6 gene . Age of onset of narcolepsy is early childhood to senescence with a peek in the teens & early 30s. Male to female ratio 1.64: 1[42]

Narcolepsy type 1 and narcolepsy type 2 are central disorders of hypersomnolence. Narcolepsy type 1 is characterized by excessive daytime sleepiness and cataplexy and is associated with hypocretin-1 deficiency. On the other hand, in narcolepsy type 2, cerebrospinal fluid hypocretin-1 levels are normal and cataplexy absent.

Diagnosing narcolepsy requires identification of all of the following[43,44,1]

Diagnostic criteria for narcolepsy types 1 and 2 (adapted from ICSD-3)

Criteria A and B must be met Narcolepsy type 1A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months

B. The presence of one or both of the following:

1. Cataplexy (as defined under 'Essential features') and a mean sleep latency of ≤8 min and two or more sleep-onset REM periods (SOREMPs) on an MSLT performed according to standard techniques. A SOREMP (within 15 min of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT
2. CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤110 pg mL1 or 110 pg mL1 or >1/3 of mean values obtained in normal subjects with the same standardized assay E.

The hypersomnolence and/or MSLT findings are not explained more clearly by other causes such as insufficient sleep, obstructive sleep apnoea, delayed sleep phase disorder or the effect of medication or substances or their withdrawal

ONSET : About 10 % of the cases can start before the age of 10 years. 5% of the cases can occur after the age of 50 yers. Usually daytime sleepiness is the first symptom , followed in months to years by other symptoms.[46]Tetrad of Narcolepsy consists of excessive sleepiness, Cataplexy, Hypnogogic hallucination, sleep paralysis.

SLEEP ATTACKS : Excessive day time sleepiness presents with unwanted & unanticipated sleep episodes lasting seconds to minutes.

Sleep attacks are irrestible & last for 10-20 minutes with dreaming. They can range from two to five episodes of sleep attacks per day resulting in functional impairments. Many patients complain of sleepiness throughout the day

CATAPLEXY: Sudden loss of muscle tone with consciousness occurs in 65%- 70% of these patients. This lasts for few seconds to minutes. The hypotonia causes sponatenous grimaces & jaw opening with tongue thrusting . Eye and respiratory muscles are spared. Cataplexy increases risk of fall & accident. Cataplexy can be precipitated by laughter, surprise, anger or excitement. Subtle forms exist with only partial loss of muscle tone.

Cataplexy is the only symptom that is specific for narcolepsy , but is present in only 70 % of the cases.The entire tetrad is present in only 10-15 % of the patients.[45]Sleep paralysis is characterized by an inability to move while still awake at sleep onset(hypnogogic) or less commonly ,on awakening(hypnopompic). Hypnogogic hallucinations are vivid sensory sensations occurring while awake at sleep onset. The sensations may include visual imagery or auditory hallucinations.Many patients complain of sleepiness throughout the day. Characteristics of of cataplexy being consciousness is always maintained during the attacks of cataplexy. The episodes rarely last more than few minutes. The weakness of cataplexy is symmetric, although weakness may involve only the muscles of the neck or face. Certain Patients report buckling knees and falling. The frequency of cataplexy is highly variable, from daily to few times a year. Episodes of cataplexy can be terminated
by hypnogogic hallucinations and then sleep.

Polysomnography reveals sleep fragmentation and often PLMS. The sleep latency is usually short , but problems in sleep maintenance are common. A short REM latency (time from sleep onset to the first REM sleep) of 20 minutes or less is the characteristic finding on polysomnography which is found only in
50% of the cases.[43,44]

A diagnosis of narcolepsy can be made by history in a patient with daytime sleepiness(daily lapses into sleep for atleast 3 months) and unequivocal
cataplexy. To rule out other sleep disorders nocturnal sleep study and multiple sleep latency are stillrecommended for confirmation . Demonstration of either a short nocturnal REM latency (<20 minutes) or MSLT performed on the following day – a mean sleep latency
<5minutes and two or more naps with
REM sleep.

MSLT testing can help support a diagnosis of narcolepsy. However a negative test does not eliminate the possibility that narcolepsy is present.A positive MSLT is not specific for narcolepsy and must be

CLINICAL FEATURES

The clinical features associated with OSA are obesity (particularly central body mass index more than 30 kg/m^2), large neck circumference (more than 40 cm), narrow mandible, narrow maxilla, retrognathia, dental malocclusion, overbite, reduced nasal patency, high and narrow hard palate, elongated and low lying uvula, enlarged tosils, enlarged adenoids and macroglossia.[14]

Clinical examination of a patient suspected to be suffering from OSA includes measurement of blood pressure, cardiorespiratory auscultation,examination of oral cavity and noting the presence of teeth and dentures. The assessment of the tonsils,tongue size, architecture of hard palate and faucal pillars are important . Mallampati score can be used to assess the upper airway in OSA.

LABORATORY DIAGNOSIS

The gold standard for the diagnosis of OSA is full polysomnography and it provides detailed information on sleep state and respiratory and gas exchange abnormalties . Other variables assessed during polysomnography are body position, heart rate and rhythm, muscle tone and contraction. Polysomnography is resource intensive requiring a full sleep laboratory and a trained technician. Aminimum of 12 channels of recordings that include electroencephalogram (EEG), electrooculogram(EOG),electromyogram(EMG), Oronasal airflow, chest wall effort, body position, snore microphone , electrocardiogram (ECG), and oxyhemoglobin saturation are usually used in polysomnographic studies.

LEVELS OF SLEEP STUDIES FOR OSAHS [20]

Level 1 : attended polysomnography – EEG,EOG,Chin EMG, airflow,effort,EKG,Sa02,leg EMG, BODY POSITION
Level 2 : unattended polysomnography same as level 1 but technologist not present
Level 3 : Cardiopulmonary study-[four or more bioparameters] Airflow, effort, Sa02,EKG, Body position
Level 4 : single or dual bioparameters –
oximetry,oximetry+ airflow or snoring

Level 1 is the gold standard & the only study recommended by American Academy of Sleep Medicine In order to determine severity of OSA several factors must be considered. Some patients with minimal saturation have frequent events, high arousal index, & severe daytime sleepiness.

If oximetry is used to screen patients for OSA , the tracing should be scrutinized for evidence of saw tooth pattern of repeated changes in Sa02. Some cases have respiratory arousal without any changes in Sa02. Certain patients with an AHI in the moderate range (15-30 /hr) have impressive arterial oxygen desaturation & low sleeping baseline Sa02.

Studies in OSA patients found that severity of nocturnal arterial oxygen desaturation was related to several factors , including awaken supine Pa02, the percentage of sleeptime spent in apnea, & the expiratory reserve volume . The
clinical significance of low expiratory reserve volume may be less obvious.

The ERV is the difference between the functional residual capacity(FRC) and the residual volume (RV).The FRC is reduced in obesity secondary to low compliance of the chest wall/abdomen. The residual volume is increased if patients have any degree of obstructive airway disease . Thus a low ERV means that the patient has low oxygen stores at the start of apnea(a low FRC) and a significant ventilation/perfusion mismatch at low lung volumes.[20,39]

SEVERITY OF OSA [20]

1. Apnea + hypoapnea index [AHI]
2. Amount of supine sleep & REM sleep in the diagnostic study
3. Respiratory arousal index
4. Severity of day time sleepiness/
requirement of alertness
5. Severity of arterial oxygen saturation
6. Sleep associated arrhythmias
7. Objective measurement of daytime sleepiness
8. Comorbid illness (Eg. Congestive heart failure, ischemic heart disease)

OBESITY & OSA

Obesity is a major risk factor for the development of OSA . Nuchal obesity is an important predictor than total body obesity.[40]

Obesity has direct effects on the upper airway function or indirect effects secondary to changes in lung volume. MRI studies of the upper airway in OSA suggested fat deposition adjacent to the lateral

pharyngeal walls reduced the upper airway size.The shape of the upper airways in OSA is different , with the lateral dimension . Weight loss increases the lateral dimension . [30]

Many patients with OSA have significant worsening of apnea in the supine position. In thisposition, gravity tends to pull the tongue backward and narrow the airway.[31]

Thus ,an overall apnea index may reflect moderate to severe when the Patient is supine and minimal apnea in the lateral decubitus body position. More than 50% of the cases with sleep apnea had AHIs atleast two times higher in the supine than in the lateral decubitusposition. Unfortunately , many obese patients with severe sleep apnea have severe apnea in the lateral decubitus position[23]

TREATMENT [33]

RDI >30/hr [RDI is defined as AHI + RERA index]{RERAs –respiratory related arousals}should be treated whether or not symptoms are present .

Symptomatic patients with RDI >5/hr also requires treatment

MILD OSA MANAGEMENT

Weight loss

Position therapy

Treatment of nasal congestion

UPPP[UVULOPALATOPHARYNGOPLASTY]

LAUP [LASE ASSISTED UVULOPALATOPHARYNGOPLASTY]

Postive airway pressure

MODERATE OSA MANAGEMENT

Positive airway pressure

UPPP[UVULOPALATOPHARYNGOPL ASTY]GAHM [GENIOGLOSSUS ADVANCEMENT HYOID MYOTOMY]

Weight loss adjunctive

Position therapy adjunctive

SEVERE OSA MANAGEMENT [34]

restorative sleep (reduced arousal, normal sleep architecture). When the AHI worsens with higher positive pressure, we need to consider the possibility that an increase in mouth/mask leak is causing the problem . A fluctuating pattern of leak without change in body position suggesta a mouth leak . Mouth leak can produce a pattern of flow resembling central[41]

Positive airway pressure
TRACHEOSTOMY GAHM
MMO [MANDIBULO MAXILLARY OSTEOTOMY][38]

Weight loss adjunctive
Reasons to treat OSA patients is to relieve symptoms of daytime sleepiness , improve the quality of life , prevent sleep disturbance endured by the bed partner and prevent long term sequelae of untreated OSA. OSA associated with atherosclerosis, hypertension[36]

Nasal CPAP is the treatment of choice for patients with moderate to severe OSA . This provides pneumatic splint to prserve upper airway patency . CPAP titration is done to determine pressure level required for airway patency: pressure is incrementally increased to find the point at which apnea, hypoapnea, snoring, desaturation and respiratory related arousal are prevented which varies from 5-20 cm H_2O among

interpreted in light of information from the prior nocturnal polysomnogram , a medication history , and the recent pattern and amount of sleep.

Patients with primary narcolepsy have a normal neurological examination. However secondary or symptomatic narcolepsy can occur in patients with head trauma, stroke, multiple sclerosis, brain tumors, neurodegenerative disorders.

Narcolepsy is associated with certain HLA markers, but genetics alone cannot explain why certain patients develop this disorder.HLA DR2 and DQ6 is commonly associated (90%)[45]. Animal studies have found that hypocretin knockout mice were found to have narcoleptic like behaviour. Dogs with canine narcolepsy – cataplexy were found to have a mutation of geneticcoding for the hypocretin -2 receptor.[46,47] In case of identical twins , when narcolepsy involves one of the pair, the other exhibits narcolepsy only in 25% of the cases. Thus a combination of genetic susceptibility and someenvironmental trigger or infectious / autoimmune disorder may ultimately determine if narcolepsy develops.[48]

FEATURES OF NARCOLEPSY IN CHILDREN

Restlessness & motor over activity may predominate .

Academic deterioration,inattentiveness & emotional lability are common Narcolepsy can be categorized as mild, moderate or severe based on the frequency of cataplexy, need for naps and disturbance of nocturnal sleep.

Narcolepsy can be classified as

1.Narcolepsy without cataplexy but with hyocretin deficiency

2. Narcolepsy with cataplexy but without hypocretin deficiency

3. Autosomal dominant cerebellar ataxia, deafness & narcolepsy

4. Autosomal dominant narcolepsy , obesity & type 2 diabetes5. Narcolepsy secondary to another medical condition Despite major advances in our understanding of narcolepsy mechanisms, its current management is only symptomatic. Treatment options may vary from a single drug that targets several symptoms, or multiple medications that each treats a specific symptom. In recent years, narcolepsy treatment has changed with the widespread use of modafinil/armodafinil for daytime sleepiness, antidepressants (selective especially at the onset of treatment. There is no evidence of tolerance [53,54]

The possibility of induction of human hepatic cytochrome P450 enzymes exists, hence an increase of the metabolism of oral contraceptives. Accordingly, the usual recommendation is for the patient to use another form of contraception while taking modafinil and for one month after stopping the medication.[56]

Modafinil is the most widely precribed drug for excessive daytime sleepiness. It is effective or very effective in 60% of serotonin and dual serotonin and noradrenalin reuptake inhibitors) for cataplexy, and sodium oxybate for both patients and partially effective in 20% Amphetamines, including d,l- [57,58]symptoms. Other psychost imulants can also be used, such as methylphenidate, pitolisant and rarely amphetamines, as third-line therapy. [49]

Modafinil :

Compared with amphetamine, modafinil has an additional phenyl (sulfinyl group) and an amide instead of an amine group, which suggests a distinct mechanism of action. However, the mode of action is still unclear even if a dopamine reuptake inhibition is very likely involved.[45,47] The elimination half-life is 13.8 hours and the maximum concentration is achieved in 2–4 hours.

Unlike previous drugs modafinil has benefited from randomized, double-blind, placebo-controlled trials, which have shown the drug to be significantly effective on excessive daytime sleepiness at a dose of 300 mg), or at doses of 200
and 400 mg [50,51,52]

The starting dose is 100–200 mg and the usual dose between 100 and 400 mg, given either as a single morning dose or as a split dose. The most common adverse effects are limited. They include headache, nausea, nervousness, and rhinitis,amphetamine, d-amphetamine (sulfate) and met-amphetamine (chlorhydrate) have been used for narcolepsy since the 1930s. At low dose, their main effect is to release dopamine – and to a lesser extent noradrenaline – through reverse efflux via monoaminergic transporters, the dopamine transporter (DAT) and the norepinephrine transporter (NET). DAT and NET move dopamine and norepinephrine, respectively, from the outside to the inside of the cell. This process is sodium dependent. At higher doses, amphetamine interacts with the vascular monoamine transporter 2 (VMAT2). The vesicularization of the monoamines (dopamine, norepinephrine, serotonine, and histamine) in the central nervous system depends on VMAT2). At a dose of 10–60 mg/day, amphetamines are very effective. However, they may be responsible for a number of adverse effects, irritability, headache, nervousness, palpitations, insomnia, and less often orofacial dyskinesia, anorexia, nausea, excessive sweating, and psychosis. Tolerance to amphetamine effect may develop in up to one third of patients[58],addiction is generally not a problem in narcoleptic patients [60]

Methylphenidate, a N-methyl derivative of amphetamine, also induces dopamine release, but does not have a major effect on monoamine storage. In comparison with amphetamines, methylphenidate has a much shorter elimination half-life (2–7 hours) [61,62]The daily dose is 10–60 mg a day. Adverse effects are the same as with amphetamines, but milder. Tolerance may develop but abuse potential is low. A sustained release form is available and can be useful in some cases.[63]

desmethylimipramine, a metabolite with adrenergic effects. Active doses are typically 25–75 mg daily. However, low doses of 10–20 mg daily are often effective, and it is always advisable to start with them to avoid anticholinergic effects.[65]

SELECTIVE SEROTONIN-REUPTAKE INHIBITORS (SSRIS)

These compounds are much more selective than tricyclic antidepress ants toward the serotonergic transporter, although most of them have affinities for other monoamine transporters at 10–100 times higher[64,65]

NON PHARMACOLOGICAL TREATMENT

In addition to pharmacological treatment, behavioral treatment measures are always advisable. Essentially, the studies available[61] support the recommendation to take planned naps during the day, as naps decrease sleep tendency and shorten reaction time. Because of limitations on work or home times, naps are best scheduled on a patient-by-patient basis.

ANTIDEPRESSANTS IN TREATMENT OF CATAPLEXY

Cataplexy was primarily treated using a tricyclic antidepressant, imipramine [63]. Tricyclic antidepressants are monoamine reuptake inhibitors but lack specificity for any single monoamine, both with respect to their parent compounds and because of the existence of active metabolites[64]

Possible mechanisms of action include anticholinergic effects, serotonergic reuptake inhibition, or adrenergic reuptake inhibition. Tricyclic antidepressants are active on cataplexy at doses below usual antidepressant dose range efficacy. Clomipramine (in Europe and Japan) and protriptyline (in the US) have been the most widely used. Clomipramine is
principally a serotonergic reuptake inhibitor, but metabolizes into concentrations.

In comparison with tricyclics, higher doses are required and effects less pronounced The daily dosage varies with the product. As a group, SSRIs possess the following adverse effects: headache, nausea, weight gain, dry mouth, erectile and ejaculation dysfunction, and decrease of libido.

NORADRENERGIC UPTAKE INHIBITORS

Viloxazine at a dose of 100–300 mg per day, reboxetine at a dose of 2–10 mg and atomoxetine at a dose of 40–60 mg per day are generally active against cataplexy.[66]

NORADRENALINE AND SEROTONIN- REUPTAKE INHIBITORS

Venlafaxine is increasingly used at a dose of 37.5–300 mg daily. The main adverse effects are gastrointestinal upset and less frequently asthma and hypertension Status cataplecticus has been reported with a shift from immediate release venlafaxine to the extended release formulation

NON PHARMACOLOGICAL TREATMENT

In contrast with excessive daytime sleepiness, there is no established behavioral treatment of cataplexy, except for avoiding situations that trigger cataplexy.

Sodium oxybate is given at a starting dose of 4.5 g/night divided into two equal doses of 2.25 g/night. The dose may be increased to a maximum dosage of 9 g/night, divided into two equal doses of 4.5 g/night, by increments of 1.5 g at 2-week intervals. Most patients will start to feel better within the first few days, but optimal response at any given dose may take as long as 8–12 weeks.[67]

The most problematic adverse effect was expected to be drug abuse. However, the monitored prescription program in the US revealed that this is a very low risk in narcoleptic patients.[68,69,70]

KLEINE –LEVIN SYNDROME

Kleine Levin Syndrome (KLS) is a rare disease with periodic hypersomnia as its main feature. Hyperphagia and hypersexuality are also described as classical symptoms, although quite recently it has become clear that the full triad is absent in the majority of patients.[71]

This condition is characterized by recurrent episodes of hypersomnia associated with cognitive and behavioral abnormalities, including confusion, apathy, irritability, megaphagia (eating increased amounts of food), and hypersexuality. Between the episodes, the sleep patterns, cognition, and behavior of patients are normal.[72]Although no population-based studies reporting on KLS prevalence are available, it is generally estimated that there are only 1.5–2.0 cases per million people.[73]

The hypersomnia may set in abruptly or slowly following several days of mounting malaise and tiredness.[74]

In Klein-Levin syndrome the sleepiness is accompanied by hyperplasia and hypersexuality. These patients sleep upto 20 hours a day , waking up only to eat and void . Some of these patients exhibit behavioral and mood changes such as disorientation, depression, confusion,hallucinations, irritability, impulsiveness and aggression as well as mild autonomic alterations.In some cases , isolated recurrent hypersomnia is the only symptom . Behavior is normal between episodes. Sleepiness typically lasts fromantic couple of days to several weeks appearing once to 10 times a year.

A prodrome such as fatigue or headache is occasionally observed. Facial blushing and perspiration may be present during an episode. Triggering events are
occasionally reported including systemic or upper airway infection , gastroenteritis, alcohol consumption, emotional distress, sleep deprivation and head trauma. Episode termination may be signaled by amnesia, dysphoria or elation with insomnia.
The majority of reported cases seen in young men and with onset in early adolescence . Prevalence is unknown and this is considered a rare disorder.

ETIOLOGY

Klein –Levin syndrome are sporadic in nature and family history is rare. However this syndrome is associated with the HLA- DQB10201 allele and homozygosity for this allele is thought to increase the risk of developing the disorder. Hypothalamic dysfunction is also postulated in this syndrome . Patients with Klein – Levin syndrome exhibits increased prolactin and thyroid stimulating hormone levels and reduced cortisol and growth hormone levels during symptomatic periods.

DIAGNOSIS

Polysomnography during an episode reveals reduced sleep efficiencies, reduced relative amount of stage REM and stage 3- 4 NREM sleep and increased relative NREM stage 1 sleep and wake time after sleep onset . Twenty hour polysomnography demonstrates prolonged total sleep time . MSLT revels short sleep latencies with SOREMPS possible in one or more naps . The absence of cataplexy distinguishes Kleine – Levin syndrome from narcolepsy [75]

TREATMENT

Stimulant medications are partially effective in Kleine – Levin syndrome. Lithium, Valproic acid, Carbamazepine and melatonin have been used as prophylactic measures

IDIOPATHIC HYPERSOMINA

Idiopathic hypersomnia presents as excessive daytime sleepiness despite adequate sleep and excluding other disorders that cause daytime sleepiness such as narcolepsy. Idiopathic hypersomnia begins in adolescence or early twenties. Patients with idiopathic hypersomnia may complain ofpersistent daytime drowsiness or discrete sleep attacks.[77]

This syndrome accounts for 5-10% of the patients seen in sleep clinics with complaints of excessive daytime sleepiness. The sleep period may be long . Some Patients are able to wake up normally , certain others report of difficulty waking and or disorientation at awakening. Unlike narcolepsy , naps are not refreshing. In some cases patients have the onset of symptoms after a viral illness such as hepatitis or mononucleosis.[78]

CLASSIFICATION[79]

Idiopathic hypersomnolence without long sleep time

A Complaint of EDS for > 3 months

B Normal nocturnal sleep < 6 h but < 10 h

C Nocturnal polysomnography has excluded other causes of EDS

D Polysomnography findings: major sleep period > 6 h and < 10 h with short sleep latency

E MSLT findings: mean sleep latency < 8 minutes and < 2 SOREMP

F Hypersomnia is not better explained by another sleep disorder, medical orneurologic disorder, mental disorder, medication use or substance abuse

Idiopathic hypersomnolence with long sleep time

A Complaint of EDS for > 3 months

B Prolonged sleep time > 10 h with laborious wakening in the morning or from naps

C Nocturnal polysomnography has excluded other causes of EDS

D Polysomnographic findings: a major sleep period > 10 h in length with a short sleep latency

E MSLT findings if performed: mean sleep latency < 8 minutes and < 2 SOREMP

F Hypersomnia is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use or substance abuse.

ETIOLOGY

Animal studies have shown destruction of feline locus coeruleus nor epinephrine neuronsresults in polysomnographic findings similar to idiopathic hypersomnia. . CSF hypocretin levels are normal . Increased thalamic spindle density has been observed in the second half of the night . The resulting increased thalamic blockade could explain the difficulty awakening and sleep drunkeness exhibited by these patients . Phase delay and possible prolongation in melatonin secretion may contribute to these symptoms.[81]

DIAGNOSIS

The clinician should look for typical features of the disorder in the absence of symptoms suggestive of other sleep or medical disorders such as behaviorally induced insufficient sleep syndrome , narcolepsy,sleep disordered breathing , restless leg syndrome, circadian rhythm abnormalities and depression .

Distinguishing narcolepsy without cataplexy from idiopathic hypersomnia with normal sleep time can be difficult. With the exception of cataplexy, the single most useful factor in the clinical history that distinguished idiopathic hypersomnia from narcolepsy was nap duration of longer than 60 minutes, which had 87% sensitivity and specificity.

Modafinil is a nonamphetamine wakefulness-promoting medication .The mean dose was 400 mg, with few patients achieving symptom control at the lower doses and 18 patients requiring greater than the licensed recommended dose (400 mg). Dexamphetamine was also effective in this group, who reported few side effects at an average dose of 30 mg per day.[82]

POSTTRAUMATIC HYPERSOMNIA

Excessive sleepiness, fatigue, headaches and cognitive impairment are the typical symptoms of post traumatic hypersomnia. They usually occur immediately following the head injury and can either persist or resolve gradually over weeks and months. Lengthy sleep episodes and frequent napping may be observed. The amount of hypersomnolence is related to the severity of the head trauma and the length of time since its occurrence. Symptoms typically improve over time with the hypersomnia resolving in approximately half of patients at one year post injury . Sleepiness is observed in 30% of the patients following traumatic brain injury.[83]

ETIOLOGY

Post traumatic hypersomnia can result from any trauma to the central nervous system, including direct blows and neurosurgical manipulation. Hypersomnia is more likely to occur following trauma to specific areas of the brain such as third ventricle, posterior hypothalamus, midbrain, or pons. CSFhypocretin -1 levels are normal in the few patients that have been tested.

DIAGNOSIS

The diagnosis is based on history of a traumatic brain injury 6 to 18 months prior to the onset of sleepiness.Head injured patients are at increased risk of developing a number of sleep disorders in addition to post traumatic hypersomnia including narcolepsy, sleep disordered breathing, nocturnal seizures and insomnia. Whiplash injuries in particular can lead to sleep disordered breathing. Nocturnal polysomnogra phy shows occasional prolonged main sleep episodes while the MSLT shows a mean sleep latency less than eight minutes with no more thanSOREMP. Twenty four hour continuous polysomnography can reveal frequent day time napping .

TREATMENT

Treatment of post traumatic hypersomniainvolves resolution of sleep disordered breathing , epilepsy or any other sleep or neurological disorder causing sleepiness resulting from head injury. Initially sleep hygiene is advocated.Stimulants like methylphenidateand somnolytic s such as modafinil can be used for sleepiness.Headache , nausea are common side effects.Many patients improve over time and may not require long term pharmacological treatment.[84]

RECURRENT HYPERSOMNIA

Recurrent hypersomnia is characterised by intermittent excessive sleepiness occurring weeks or months apart . Klein-Levin syndrome and menstrual related hypersomnia present with recurrent hypersomnia.[85]

Menstrual related hypersomnia involves recurrent sleepiness temporally related to menses.The onset of this disorder is typically just after menarche with episodes lasting about a week and terminating abruptly. Sleep and alertness are normal both before and after the menstrual period. Diagnosing recurrent hypersomnia involves the appropriate clinical history in the absence of another medical cause for these symptoms . Elevated prolactin levels are seen in menstrual related hypersomnia. Reduced hypothalamic dopaminergic tone and possible impairment of other monoaminergic pathways in Klein – Levin Syndrome . and menstrual related hypersomnia.[86]

BEHAVIOURALLY INDUCED INSUFFICIENT SLEEP SYNDROME

Insufficient sleep syndrome results when an individual consistently fails to obtain sufficient nocturnal sleep to support normal alert wakefulness.[87]

The resulting chronic sleep deprivation is therefore voluntary and unintentional . Although sleep need varies from person to person , most would agree that seven to nine hours of sleep per night is needed to avoid excessive sleepiness.[88]These path develop a persistent sleep debt by chronically obtaining less than optimal amount of sleep. Chronic sleep restrictionresults in sleepiness, irritability, concentration and attention deficits , reduced vigilance, distractibility, fatigue, restlessness and malaise .[89,90]

Further more sleep deprivation has been shown to increase mortality, alter metabolic , endocrine and immune function and impair psychomotor vigilance task performance equal to legal intoxication.[91]

The exact prevalence and incidence of insufficient sleep syndrome , although more common in men is not known, It occur more frequently in adolescence , where social pressure and delayed sleep phase issues combine to curtail sleep. Insufficient sleep is the most common cause of sleepiness in the society.[92]

ETIOLOGY

Insufficient sleep is a volitional failure to obtain the needed amount of sleep and as such etiology is self imposed. . The deprioritization of sleep in our society has many causes including artificial light, television, social media, shift work and economic causes

TREATMENT

Patient education regarding sleep prioritization. Sleep hygiene should be emphasized. Explaining the risks of sleep deprivation with regards to motor vehicle accidents , impaired workplace performance and disrupted interpersonal relationships can help change behaviour.[93]

ORGANIC CAUSES OF HYPERSOMNIA

Sustained drowsiness is characteristic or periods of sleep greatly in excess ofnormal requirements . Lesions involving the midbrain tegmentum or posterior hypothalamus are a common cause. Hypothalmic lesions prsents with excessive hunger, weight gain, Polyuria, polydipsia and somnolence .

Prolonged hypersomnia may follow encephalitis lethargica, general paresis or cerebral edema from any cause. Infective processes such as encephalitis, thyphoid, trypanosomiasis or tuberculous meningitis are regularly accompanied by somnolence. Prolonged and disabling daytime sleepiness following infectious mononucleosis .[95]

Uraemia (Metabolic disorders)present with somnolence , similarly the encephalopathies associated with anoxia,chronic respiratory insufficiency or hepatic disorder.[94]Endocrine causes are hypothyroidism, Cushing's and addison's disease,diabetes mellitus and hyperinsulinism .Rarer causes industrial toxins and lead encephalopathy. Prolonged hypersomnia has been found following the administration of combined oral and depot neuroleptics, persisting for several months after discontinuation.[96,97]

HYPERSOMNIA ASSOCIATED WITH MOOD DISORDERS

Hypersomnia commonly occurs in patients and is associated with treatment resistance, symptomatic relapse, increased risk of suicide and functional impairment. Genes pertinent to hypersomnia in mood disorders are those related to MAO –A gene. The role of glucocorticoids in the transcription and subsequent activity of MAO –A.[98]

Hypersomnia symptoms associated with mood disorders are not specific and may include non-imperative EDS, long non- refreshing naps, long sleep time, and sleep inertia.[99]EDS should be distinguished from insufficient sleep and fatigue. Fatigue is not necessarily relieved by increased sleep and may be unrelated to sleep quantity or quality. However, it is difficult to differentiate between EDS and fatigue, which may overlap considerably in mood disorders. It is also particularly difficult to differentially diagnose between idiopathic hypersomnia and less severe forms of depression like dysthymia.[100] Symptoms of depression with atypical features include the following:

A. Mood reactivity (i.e., mood brightens in response to positive events)
B. Two or more of the following features, present for most of the time, for at least two weeks:
1. Increased appetite
2. Increased sleep
3. Leaden paralysis (i.e., heavy, leaden feelings in arms or legs)
4. Interpersonal rejection sensitivity (not limited to episodes of mood disturbance) resulting in significant social or occupational impairment
C. Criteria are not met for melancholic or catatonic features of depression.

Modafinil and armodafinil which are approved for the treatment of excessive sleepiness.[101,102]

Excessive sleepiness is common inour society. The astute physician should have a broad differential diagnosis. A through sleep history, overnight polysomnography and in some cases MSLT, 24 hourpolysomnography, wrist actigraphy and cerebrospinal fluid hypocretin -1 levels are helpful in making a diagnosis. Treatment should involve patient education, stimulants and in the case of narcolepsy, anti cataplectics. Emotional support from both physicians and support groups is critical to the overall well being of the patient.

REFERENCES

[1] American Academy of Sleep Medicine. International Classificati on of Sleep Disorders, 3rd Edition: Diagnostic and Coding Manual. Westchester, IL: American Academy of Sleep Medicine. 2014

[2]. Besset A. Assessing sleepiness. In: Billiard M, ed. Sleep: Physiology investigations and Medicine. New York, NY: Kluwer Academic/Plenum Publishers. 2003:169–184.

[3] Billiard M., Dauvilliers Y. Narcolepsy In: Billiard M, ed. Sleep: Physiology Investigations and Medicine.New York, NY: Kluwer Academic/Plenum Publishers. 2003:403–406.

[4] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep.1991;14:540–545.

[5] Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: a new approach. Psychophysiol. 1973;10:431– 436.

[6]. Eckert DJ, Jordan AS,Merchia P. Central sleep apnea: Pathophys iology and treatment .Chest 2007;131:595-607.

[7.] Burwell CS,Robin ED, Whaley RD. Extreme obesity associated with alveolar hypoventilation: a Picwickian syndrome . Am J Med 1956;21:811-818.[8].L u i M M , Lam JC, Mak HK et al. C- reactive protein is associated with obstructive sleep apnea independent of visceral obesity. Chest 2009;135:950-956

[9] Young T,Palta M, Dempsey J. The occurrence of sleep disordered breathing among middle aged adults. N Engl J Med 1993;328:1230-1235.

[10] Young T, Skatrud J, Peppard PE . Risk factors for obstructive sleep apnea in adults . JAMA 2004;291:2013-2016.

[11] Eckert D, Malhotra A. Pathophysiology of Adult obstructive sleep apnea. Proc Am Thorac Soc 2008;5:144-153.

[12]. Wolf J,Lewicka J, Narkiewicz K. Obstructive sleep apnea: an update on mechanisms and cardiovascular consequences. Nutr Met Cardiovasc Dis 2007;17:233-240.

[13] Ip MS,Lam B, Chan LY et al.Circulating nitric is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive airway pressure. Am J Respir Crit Care 2000;162:2166- 2171.

[14] Prabhakar R. Sleep apneas :An oxidative Stress ?Am J Respir Crit Care Med 2002 ;165:859-860.[15]Golbin JM, Somers VK , Caples SM. Obstructive sleep apnea , Cardiovascular Disease and Pulmonary Hypertension. Proc Am Thorac Soc 2008 ;5:200-206.

[16] Svatikova A, Wolk R, Lerman LO et al. Oxidative stress in Obstructive sleep apnea . Eur Heart J 2005;26:2435-2439.

[17] Dyugovskaya L, Lavie P, Lavie L . Phenotypic and functional characterization of blood T cells in sleep apnea.2003;168:242-249.

[18] Dyugovskaya L, Lavie P, Hirsh M, Lavie L. Activated CD8 + T lymphocytes in obstructive sleep apnea . Eur Respir J .2005;25:820-828.

[19] Tasali E, Ip MS .Obstructive Sleep Apnea and Metabolic Syndrome Alterations in Glucose Metabolism and Inflammation . Proc Am Thorac Soc .2008 ;5:207-217.

[20] Mc Nicholas WT . Diagnosis of Obstructive sleep apnea in Adults . Proc Am Thorac Soc . 2008;5;154-160.

[21] Philips BG, Kato M, Narkiewicz K et al. Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea . Am J Physiol Heart Circ Physiol 2000;279:H234-H237.

[22] Lam JCM, Mak JCW, Ip Ms. Obesity , obstructive sleep apnea and metabolic syndrome.Respirology2013;17:223-236.

[23] Rama A, Tekwani S, Kushida C. Sites of obstruction in obstructive sleep apnea . Chest 2002;122:1139-1147.

[24] Lumeng JC, Chervin RD . Epidemiology of pediatric obstructive sleep apnea . Proc Am Thorac Soc 2008;5(2):242-252.

[25] Hwang SH , Guilleminault C, Park CS et al. Usefulness of adenotonsillar size for the prediction of severity of obstructive sleep apnea and flow limitation. Otolaryngol Head Neck Surg 2013;149 (2):326-344.

[26] Walker R. Long-term health consequees of mild to moderate obstructive sleep apnea . Arch Otolaryngol Head Neck Surg2001; 127:1397-1400.b

[27] Sogut A, Altin R, Uzun L et al.Prevalence of obstructive sleep apnea syndrome and associated symptoms in 3- 11year old Turkish children. Pediatr Pulmonol 2005 ;39:251-256.

[28] Marcus CL, Curtis S, Koerner CB et al. Evaluation of pulmonary function and polysomnography in obese children and adolescents. Pediatr Pulmonol 1996;21:176-183.

[29] Capdevila OS, Kheirandish – Gozal L, Dayyat E et al. Pediatric Obstructive sleep apnea: complications, management and long term outcomes . Proc Am Thorac Soc 2008 ;5 (2):274-282.

[30] Villa MP, Brunetti L,Bruni O et al. Guidelines for the diagnosis of obstructive sleep apnea syndrome . Minerva Pediatr 2004 ;56:239-253.

[31] Bradley TD et al. Obstructive sleep apnea and its cardiovascular consequences . Lancet 2009; 373:82-90.

[32] Eckert DJ et al.Central sleep apnea :Pathophysiology and treatment . Chest 2007;131:595-611.

[33] Engelman HM et al. Randomized crossover trial of two treatments for sleep apnea / hypoapnea syndrome: Continous positive airway pressure and mandibular repositioning splint.Am J Respir Crit Care Med 2002;165:855-870.[34]Marin JM et al : Long term cardiovascular outcomes in men with obstructive sleep apnoea-hpoapnea with or without treatment with continuous positive airway pressure:An observational study 2005;365:1046-1060

[35] Pack AL et al :Risk factors for excessive sleepiness in older adults . Ann Neurol 2006;59:893-903.

[36] Carskadon MA., Dement WC., Mitler MM., Roth T., Westbrook PR., Keenan S. Guidelines for the Multiple Sleep Latency test (MSLT): a standard measure of sleepiness. *Sleep.* 1986;9:519–524

[37] SomersVK et al:Sleep apnea and vascular disease. Circulation 2008;118:1080-1099.

[38] Sundaram S et al :Surgery for obstructive sleep apnoea in adults . Cochrane Database Syst Rev 2008, Cd001004

[39] Whitelaw WA et al : Clinical usefulness of home oximetry compared with polysomnography for assessment of sleep apnea. Am J Respir Crit Care Med 2005;171:188-190.

[40] Yaggi HK et al.Obstructive sleep apnea as a risk factor for stroke and death . N Engl J Med 2005;353:2034-2037.[41]Young T et al. Sleep Disordered breathing and mortality :Eighteen year follow up of the Wisconsin sleep cohort . Sleep 2008;31:1071-1080.

[42] Geladi JM,Brown JW.Heriditary cataplexy . Journal of Neurology , Neurosurgery and Psychiatry 1967;30:455- 457.

[43] Arand D, Bonnet M, Hurwitz T, Mitler M, Rosa R, Sangal RB. The clinical use of the MSLT and MWT. Sleep. 2005;28:123– 144

[44] Doghramji K, Mitler MM, Sangal RB, Shapiro C, Taylor S, Walsleben J, Belisle C, Erman MK, Hayduk R, Hosn R, O'Malley EB, Sangal JM, Schutte SL, Youakim JM. A normative study of the maintenance of wakefulness test (MWT) Electroencephalogr Clin Neurophysiol. 1997;103:554–562

[45] Mignot E, Hayduk R, Black J et al.HLA DQB1*0602 is associated with cataplexy in 509 narcoleptic patients . Sleep 1997;20:1012-1020.

[46] De Lecea L. Kilduff TS, Peyron C et al.The hypocretins :Hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci USA 1998;95:322- 327.

[47] Nishino S, Ripley B, Overeem S. Hypocretin (Orexin) defiency in human narcolepsy . Lancet 2000;355:39-40.

[48] Thannickal TC, Moore RY, Nienhius R. Reduced number of hypocretin neurons in human narcolepsy . Neuron 2000;27:469-474.

[49] Lockrane B., Bhatïa P., Gore R. Successful treatment of narcolepsy and cataplexy: a review. Can Respir J. 2005;12:225–227.

[50] Mignot E, Nishino S, Guilleminault C, et al. Modafinil binds to the dopamine uptake carrier site with low affinity. Sleep. 1994;17:436–7.

[51] Nishino S, Kanbayashi T. Symptomatic narcolepsy, cataplexy and hypersomnia, and their implications in the hypothalamic hypocretin/orexin system. Sleep Med Rev. 2005;9:269–310.[52]Wisor JP, Nishino S, Sora I, et al. Dopaminergic role in stimulant induced wakefulness. J Neurosci.2001;21:1787–94.

[53] Broughton R, Ghanem Q, Hishikawa Y, et al. Life effects of narcolepsy in 180 patients from North-America, Asia and Europe compared to matched controls. Can J Neurol Sci. 1981;8:299–304.

[54] Moldofsky H, Broughton RJ, Hill JD. A randomized trial of the long-term, continued efficacy and safety of modafinil in narcolepsy. Sleep Med. 2000;1:109–16.

[55] Aldrich MS. The clinical spectrum of narcolepsy and idiopathic hypersomnia. *Neurology.* 1996;46:393– 401.

[56] Thorpy MJ, Black J, Erman MK. The safety profile of modafinil in disorders of sleep and wakefulness. Neurology. 2004;62(Suppl 5):A56–7.

[57] Prinzmetal M, Bloomberg W. The use of benzedrine for treatment of narcolepsy. JAMA.1935;105:2051–4.

[58] Mitler MM, Aldrich MS, Koob GF, et al. Narcolepsy and its treatment with stimulants (ASDA standards of practice) Sleep. 1994;17:352–71.

[59] Mitler MM, Shafor R, Hajdukovik R, et al. Treatment of narcolepsy:objective studies on methylphenidate, pemoline,and protriptyline. Sleep. 1986;9:260–4.

[60] Guilleminault C, Mancuso J, Quera- Salva MA, et al. Viloxazine hydrochloride in narcolepsy:a preliminary report. Sleep. 1986;9:275–79.

[61] Rogers AE, Aldrich MS, Lin X. Comparison of three different sleep schedules for reducing daytime sleepiness in narcolepsy. Sleep. 2001;24:385–91

[62] Broughton R, Ghanem Q, Hishikawa Y, et al. Life effects of narcolepsy in 180 patients from North-America, Asia and Europe compared to matched controls. Can J Neurol Sci. 1981;8:299–304.

[63] Akimoto H, Honda Y, Takahashi Y. Pharmacotherapy in narcolepsy. Dis Nerv Syst. 1960;21:1–3.

[64] Tatsumi M, Groshan K, Blakely RD, et al. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur J Pharmacol. 1997;340:249–58.

[65] Schachter M, Parkes JD. Fluvoxamine and clomipramine in the treatment of cataplexy. J Neurol Neurosurg Psychiatr. 1980;43:171–4.

[66] Nishino S, Kanbayashi T. Symptomatic narcolepsy, cataplexy and hypersomnia, and their implications in the hypothalamic hypocretin/orexin system. Sleep Med Rev. 2005;9:269–310.

[67] Nishino S, Mao J, Sampathkumaran R, et al. Increased dopaminergic transmission mediates the wake-promoting effects of CNS stimulants. Sleep Res Online. 1998;1:49–61.

[68] Nishino S, Mignot E. Pharmacological aspects of human and canine narcolepsy. Progr Neurobiol.1997;52:27– 78.

[69] Larrosa O, de la Llave Y, Bario S, et al. Stimulant and anticataplectic effects of reboxetine in patients with narcolepsy. Sleep. 2001;24:282–5.

[70] Niederhofer H. Atomoxetine also effective in patients suffering from narcolepsy? Sleep. 2005;28:1189.

[71] Critchley M, Hoffman HL. The syndrome of periodic somnolence and morbid hunger (Kleine-LevinSyndrome) Br Med J. 1942;1:137–9. doi: 10.1136/bmj.1.4230.137.

[72] Reimão R, Shimizu MH. Kleine- Levin syndrome. Clinical course, polysomnography and multiple sleep latency test. Case report. Arq Neuropsiquiatr. 1998;56:650–4. doi: 10.1590/S0004-282X1998000400021.

[73] Arnulf I, Zeitzer JM, File J, Farber N, Mignot E. Kleine-Levin syndrome:A systematic review of 186 cases in the literature. Brain. 2005;128(Pt 12):2763– 76. doi: 10.1093/brain/awh620.

[74] Arnulf I, Lin L, Gadoth N, File J, Lecendreux M, Franco P, et al. Kleine- Levin syndrome:A systematic study of 108 patients. Ann Neurol. 2008;63:482– 93. doi: 10.1002/ana.21333.

[75] Rosenow F, Kotagal P, Cohen BH, Green C, Wyllie E. Multiple sleep latency test and polysomnography in diagnosing Kleine-Levin syndrome and periodic hypersomnia. J Clin Neurophysiol. 2000;17:519–22

[76] Gallinek A.The Klein –Levin Syndrome:hypersomnia, bulimia and abnormal mental states . World Neurology 1962;3:235-243.

[77] Kirstie N. A, , Samantha P, [1] Linda D. S, Idiopathic Hypersomnia: A Study of 77 Cases.Sleep. 2007 Oct 1; 30(10): 1274– 1281.

[78] Leu-Semenescu S, Quera-Salva MA, Dauvilliers YFrench consensus. Idiopathic hypersomnia: Investigations and follow-up.Rev Neur (Paris). 2016 Nov 9. pii: S0035-3787(16)30274-0. doi: 10.1016/j.neurol.2016.09.015. [Epub ahead of print]

[79] Billiard M.Diagnosis of narcolepsy and idiopathic hypersomnia. An update based on the International classification of sleep disorders, 2nd edition.Sleep Med Rev. 2007 Oct;11(5):377-88.

[80] Honda Y, Honda M.Idiopathic hypersomnia--review of literatures and clinical experiences on 16 Japanese casesNihon Rinsho. 1998 Feb;56(2):371-5

[81] Nevsimalova S, Blazejova K, Illnerova H. A contribution to pathophysiology of idiopathic hypersomnia. Suppl Clin Neurophysiol 2000;53:366-370.

[82]. Brooks S,Mignot E. Narcolepsy and idiopathic hypersomnia. In :Lee-Choing T, Sateia MJ, Carskadon M, eds. Sleep Medicine . Philadelphia:Hanley and Belfus ,2002:193-201.

[83] Guilleminault C, Faull KF, Miles L. Post traumatic excessive daytime sleepiness :a review of 20 patients. Neurology 1983:33(12):1584-1589.

[84] Guiileminault C, Yuen KM, Gulevich MG. Hypersomnia after head-neck trauma: a medicolegal dilemma. Neurology 2000:54(3):653-659.
[85] Chung KF. Recurrent hypersomnia : a case report with polysomnographic findings . Hong Kong Med J 1997;3(1):107-110[86]Bamford CR. Menstrual –associated sleep disorder:an unusual hypersomniac variant associated with both menstruation and amenorrhea with a possible link to prolactin and metoclopramide . Sleep 1993:16 (5)484-486.
[87] Curcio G, Ferrara M, De Gennaro L. Sleep loss, learning capacity and academic performance. Sleep Med Rev. 2006;10:323–37.
[88] Eliasson A, Eliasson A, King J, Gould B, Eliasson A. Association of sleep and academic performance. Sleep Breath. 2002;6:45–8.
[89] Johns MW, Dudley HA, Masterton JP. The sleep habits, personality and academic performance of medical students. Med Educ. 1976;10:158–62.
[90] Liu X, Zhou H. Sleep duration, insomnia and behavioral problems among Chinese adolescents. Psychiatry Res. 2002;111:75–85.
[91] Park S, Cho MJ, Chang SM, et al. Relationships of sleep duration with sociodemographic and health-related factors, psychiatric disorders and sleep disturbances in a community sample of Korean adults. J Sleep Res. 2010;19:567– 77.
[92]. Lee YJ, Cho SJ, Cho IH, Kim SJ. Insufficient sleep and suicidality in adolescents. Sleep. 2012;35:455–60.
[93] Dement WC, Mitler MM. Its time to wake up to the importance of sleep disorders. JAMA
[94] M. Weiner and F. H. Epstein.Signs and symptoms of electrolyte disorders.Yale J Biol Med. 1970 Oct; 43(2): 76–109.
[95] Guilleminault C,Mondini S.Mononucleosis and chronic day time