Sleep disorders

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Journal of the Ceylon College of Physicians, 1996, **29/2**, 47-56

Although still in evaluation, the clinical discipline of sleep and its disordres is becoming increasingly linked to dysfunction of the brain with modulation by hormones, neuro-transmitters and active peptides.

Wakefulness and sleep are antagoinst states competing for domain of brain activity. The neuronal system that control this sleep-wake is found in the brain stem, hypothalamus and basal forebrain with relay nuclei in the thalamus and the target organ in the cortex. During sleep distinct stages of REM sleep and Non REM sleep alternate in a well organised fashion. REM sleep is characterised by Rapid eye movement, Muscle atonia and dream content. REM sleep for example originates in brainstem centres. It is generated in different areas of the Pons and caudal midbrain. The function of REM sleep remains as mysterious as ever. In REM sleep muscle atonia occurs with activity in the peri locus ceruleus area of the pons. This stimulates the inhibitory cells of the magnocellular reticularis nucleus of the medulla via the Tegmento-reticular Tract. This inhibits the spinal motor neurones causing atonia. Bilateral interruption of Tegmento reticular Tract (TTR) in the Pons or perilocus ceruleus area leads to REM sleep without atonia, a condition that facilitates dream enactment. This occurs in lacunar infarcts in brainstem or in olivo ponto cerebellar degeneration (TTR destroyed). There is bizarre motor activity with screaming and patient recalls dream[1]. Polysomagram shows REM without atonia.

Ponto geniculo occipital (PGO) spikes are generated phasically in REM by the dorsolateral pontine tegmentum known as area X. This PGO spikes facilitates Rapid eye movement. PGO activity may eventually reach cortical areas and trigger fragmentary imagery that we recognise as dreams. Rapid eye movements which is the hallmark of REM Sleep is produced by stimulation of the periabducens area of the dorsomedial Pons. Lesion studies have shown that PGO spikes, atonia and EEG desynchrony can be individually dissociated from REM sleep state. Conversely, stimulation studies have shown that each of these phenomena can be separately evoked. Intrusion of components of one state into another may cause severe symptoms. Cataplexy is an example of such dissociation of REM sleep components. REM sleep atonia intrudes into wakefulness. Here a strong emotion like laughter, instead of producing arousal triggers the REM sleep atonia mechanism during waking due to malfunctioning of cells controlling muscle tone.

The classification of sleep disorders has been of particular interest to sleep specialists since the rapid expansion of the field of sleep medicine. The earlier classification was symptom based but formed the basis of modern classifications. International classification of Sleep disordres (ICSD) was produced after a 5 year process initiated by the American Sleep disorders association. This classification replaces and updates the Diagnostic classification of sleep and Arousal disorder published in 1979.

A useful diagnostic classification divides sleep disorders symptoms as

(1) Disorders of initiating and maintaining sleep (DIMS)
(2) Disorders of Excess Somnolence (DOES)
(3) Disorders of Sleep wake schedule
(4) Parasomminias – Dysfunction associated with sleep, or partial arousal.

Prevalence of some Sleep disorders[2] (British figures) is given in Fig 1.

Dissociated states of wakefulness and sleep:

We spend our lives in 3 different states of being. This is wake, Non REM sleep and REM sleep. The states can oscillate rapidly resulting in bizarre and important clinical syndromes (Fig 2).

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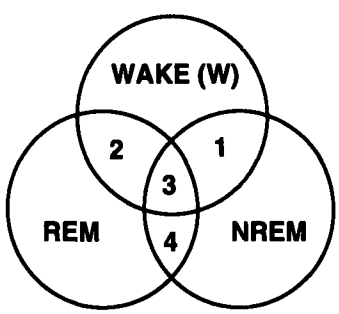
Impact of Some Sleep Disorders

Prevalence of some sleep disorders

Narcolepsy	0.15%
OSA	2%
Restless Leg syndrome	5 - 15%
Shift Worker Sleep Disorder	2 - 5%
Sleep Walking	1 - 15%
Insomnia	30% (severe in 10%)
Snoring	40 - 50% after 65 years
Sudden Infant Death Syndrome	1 - 2 / 1000 live births
Parkinsonism :	60 - 90% have sleep problems

Figure 1. Shows prevalence of some commonly known sleep disorders. (British figures). Sleep problems in Parkinsonism is highlighted.

Areas of Overlap Among States



I	W-NREM	-	Arousal Disorders : Sleep : Drunk, Walking, Terror
II	W-REM	-	Cataplexy, Hypnogogic Hallucination, Sleep Paralysis
		-	RBD
		-	Delirium (Hallucination)
III	W-NREM-REM	-	Status Dissociatus

Figure 2. Shows how intrusion of components of one state into another could cause symptoms.

Dissociation from prevailing wakefulness:-

Components of REM intrusion into wake accounts for many symptoms of narcolepsy–

In Sleep paralysis and cataplexy, REM sleep atonia intrudes into wake state. REM dreaming appearing on the transition between wake and sleep produces hypnogogic hallucination.

Wakeful dreaming causes the vivid hallucination of delirium tremens.

NREM sleep intrusion into wake occurs as microsleep periods interrupting wake state. Patient is wake enough to perform complex behaviours but Sleep enough not to be aware of the acts. Such automatic behaviour can be mistaken for complex partial seizures. Legal implication are possible for driving on wrong side of road or causing accidents.

Dissociation from NREM Sleep – Wake intrusion into NREM sleep is disordered arousal. In Sleep drunkenness there is confusional arousals seen during transition from NERM sleep to wakefulness. More dramatic disorders of arousal include Sleep walking and Sleep Terror. These spectrum of behaviour is called "disordres of Arousal".

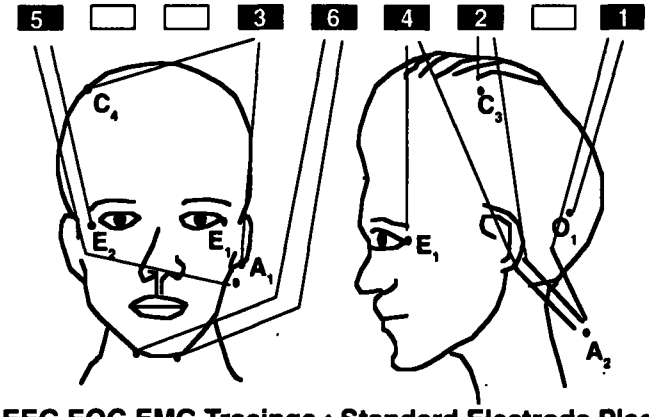
Dissociation from REM Sleep – The most prominent dissociated state arising from REM sleep is REM sleep behaviour disorder (RBD) in which muscle tone of wake state persists during REM sleep. The preservation of motor tone in patients with RBD permits vigorous and injurious motor activity by acting out dreams.

Wake – REM – NREM Sleep admixtures: A syndrome called status dissociates has been described in humans, that appears to represent a complete breakdown of state-determining boundaries.

The appearances of state dissociation may be the initial manifestation of underlying neuropathology. RBD could present 5 years before Parkinson disease symptoms occur.

Polysomnogram: This is the technology used in diagnosing sleep disorders and is a relatively new field. Sleep laboratory includes a private comfortable bedroom for each patient and a central control room for equipment and for the staff to perform on-line monitoring. The bedrooms should be sound and light attenuated. The polysomnographic test used to study sleep disorders consist of night time polysommnography (PSG) and the multiple sleep latency test (MSLT) which measures daytime alertness.

Sleep is monitored by the 3 physiological signals, Electroencephalogram (EEG), Electrooculogram (EOG) and Electromyogram (EMG) over the chin muscle. (Fig 3).



EEG.EOG.EMG Tracings : Standard Electrode Placement

E.E.G 1 (O1 - A2)
2 (C3 - A2)
3 (C4 - A1)
E.O.G 4 (E1 - A2)
5 (E2 - A1)
E.M.G 6 Chin

Caption:
O : Occipital Area
C3 : Left Rolandic Area
C4 : Right Rolandic Area
O1 : Left Occipital Area
A1 : Left Mastoid Reference
A2 : Right Mastoid Reference
E1-E2 : Left-Right Eye Outer Canthi

Figure 3. Shows electrode placement to monitor EEG, EOG and EMG.

Sleep related breathing disorders are monitored by airflow, chest and abdominal movements, oximeter snoring and this is related to sleep and body position (Fig 4). A microphone detects snoring. Additional paramaters monitored are ECG and leg movements. Audiovisual monitoring using video is done to see abnormal behaviour in sleep in parasomnia. These events are time locked to the physiological signals. The resulting polysomnogram consists of at least 1000 pages or epochs of 30 seconds of wave form data for analysis and interpretation. The reason for recording the EOG is for recording the cardinal sign of Rapid eye movement (REM) sleep. Sleep is staged into 5 stages[3] NREM stages 1-4 and REM sleep. Sleep is scored and summarised into a comprehensible form of a hypogram of the whole night events. Computers are a great boon in polysomnography in order to extract and analyse mountains of data. The delta, theta, alpha sleep waves and spindles in the EEG, the EMG and eye movements are counted for sleep staging. A user formattable report can be generated in minutes.

In our laboratory we use a computer to assist in scoring sleep, recognise and classify respiratory events and leg movements and align these to sleep, arousals, body position.

In our Sleep clinic, were see more Hypersomnia than Insomnia as a complaint. One very common causes of hypersomnia is sleep related breathing disorder.

Sleep related breathing disorders: Respiration can be affected severely by the transition from wake to sleep with devastating consequences on daytime alertness. Cessation of breathing during sleep can be due to obstructive sleep apnoea (OSA) where there is obstruction to the upper airway or it could be due to central apnoea where there is a loss of respiratory effort. In OSA we see a mixture of Central and obstructive apnoea. The cumulative effect of apnoea and hypopnea on the patients health is being realised only recently. Previously we associated apnoea with severely obese patients of Pickwickian syndrome. We now recognise normal weight snorers with sleep apnoea.

Incidence of OSA in the general population is not known. Figures of 1% to 24% have been mentioned in studies from Israel[4] and Wisconsin[5] respectively. From our studies in Singapore we suspect that the actual figure is higher.

In OSA the patients sleep is repeatedly disrupted by apnea. The apnea could happen as many as 40 to 50 times each hour (Apnoea Index). Each apnoea could last 60 seconds or more causing anoxia and is ife threatening. Patients are at increased risk for accidents due to excessive daytime sleepiness (EDS), high blood pressure, heart attack, stroke and corpulmonale. They feel unfresh, have early morning headaches and the males could develop impotence.

Objective evaluation of sleep and apnoea is by polysomnography performed overnight in a sleep Laboratory (Fig 4). Daytime sleepiness is assessed objectively by the multiple sleep latency test which follows the overnight test.

Snoring is the commonest way the patients with OSA present[6]. We studied the problems of snoring in a Singapore population (Fig 5) and found that 77.2% of the adults were snorers. 41.8% of the population were habitual loud snorers. Snoring is the most common reason for referral for Sleep study. The snoring cou d ger erate 60-80db of noise (as much as a Pneumatic drill smashing concrete). It is not surprising that snorers make intolerable bed partners and this had been a reason for divorce among married couples. 87.5% of loud habitual snorers were found to have OSA on poly-somnography (F g 5). 95% of OSA were seen in stage 1 and 2 Sleep. Male to female ratio was 9:1. Excess daytime sleepiness (EDS) occurred in 80.0% of OSA cases. When objectively assessed by MSLT 92.5% of OSA cases had EDS. When we analysed the sleep architecture of these OSA patients it was obvious that EDS occurred in patients who had very poor slow wave sleep due to frequent arousals by the apnoic attacks. The OSA patients who had motor accidents while driving due to EDS were found to have high AI, absent slow wave sleep (Delta wave) and many arousals. The overwhelming complaint of EDS is therefore due to the patients being unable to reach delta sleep and to the many arousals causing sleep fragmentation. EDS in our patients improved with treatment by nasal Continuous Positive Airway Pressure (CPAP). There was reversal of sleep fragmentation with decrease in arousal. Delta sleep increased, this being important for recovering of EDS.

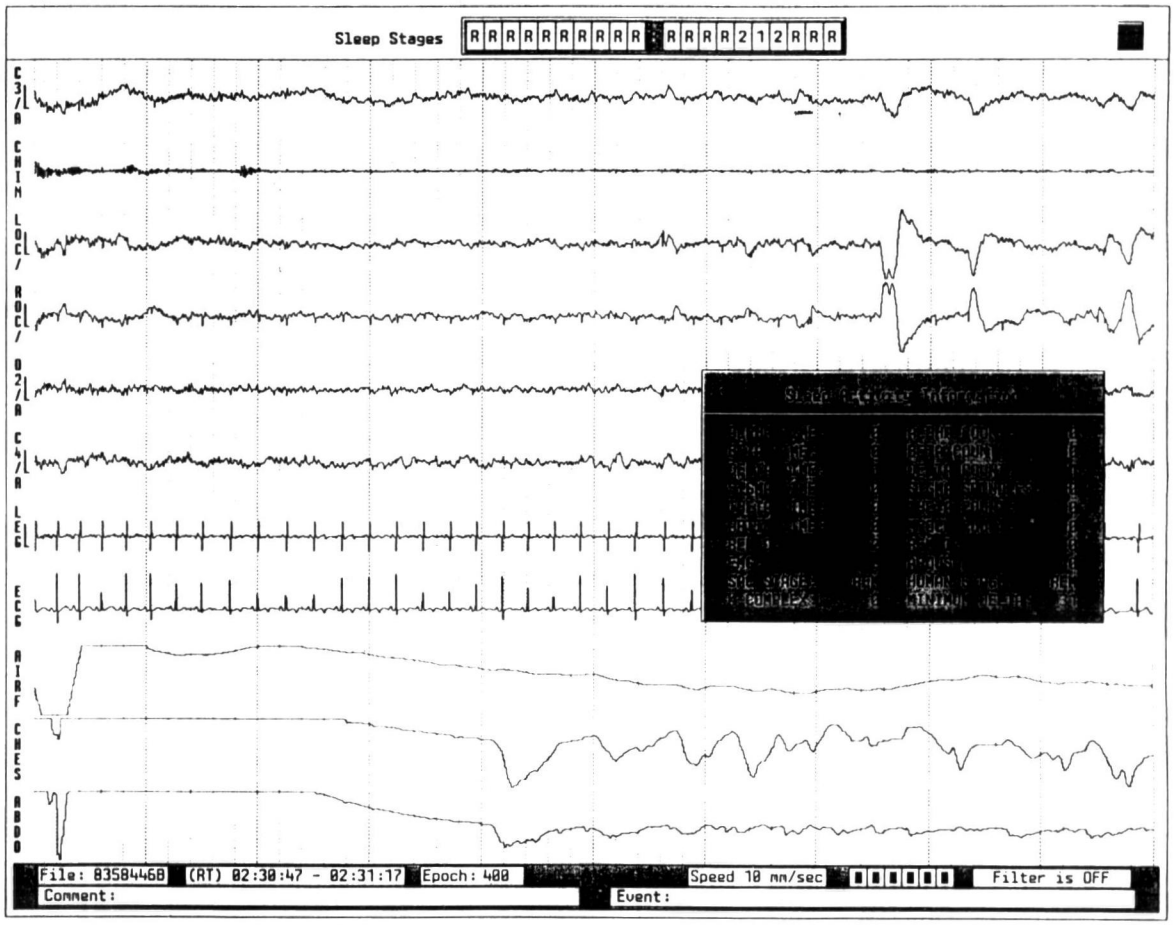


Figure 4. A 30 second epoh of the hypnogram showing mixed apnoea in REM sleep. The EEG, Chin EMG, eye movements in left (Loc) and right (roc) outer canthus are shown in the first to fourth graphs. Note the rapid eye movements (REM) shown in LOC & ROC leads and the atonia in chin EMG. The airflow, chest and abdominal movements are shown in the last three graphs.

Snoring in A Singapore Population - Partners Interviewed

	M	F	Total	Age
No. Subjects	(114)	(106)	(220)	(20 - 80 yr)

- **Snorers** 170 (77.2%)
- **Loud habitual snorers** 92 (41.8%)
- **Spouse separated** 5
- **Apnea observed** 91
- **Excessive daytime sleepiness (in snorers)** 63 (37.05%)

Figure 5. Snoring in a Singapore population.

Snoring and Obstructive Sleep Apnea (OSA) in a Singapore Population

	Total	M	F	Age	Apnea Index
Loud habitual snorers	80	72	8 (9:1)	20-73 yrs	
OSA	70 (87.5%)				5.1 - 85
Hypersomnia in OSA (History)	56 (80.0%)				
Hypersomnia in OSA					
MSLT studied	27				
Hypersomnia on MSLT	25 (92.5%)				

Figure 6. Snoring and OSA in a Singapore population.

The improvement in snoring and the apnoea with CPAP is dramatic. Currently surgery for snoring and OSA for our patients is Uvulo Palatopharynoplasty (UPPP). Recently our ENT surgeons have started performing Laser assisted uvulopalatoplasty for treatment of snoring and OSA. The advantage of this is that it can be performed under local anaesthesia in our ambulatory surgery centre.

Non obstructive (Central and Neuromuscular) sleep apnoea – Any lesion affecting the respiratory loop from chemoreceptors to sensory pathway, brainstem, descending motor pathway, spinal motor neurone, motor nerves, neuromuscular junction and muscles will lead to abnormal breathing pattern.

There are many diseases of Neurological origin that can lead to hypoventilation and central apnoea during sleep before any respiratory abnormality is evident in wakefulness. This is because respiration in sleep is so directly influenced by the metabolic control system. The REM related inhibition of intercostal and accessory muscles leads to profound hypoventilation.

We studied dystrophia myotonica patients (Fig 7) because they often complain of excessive daytime sleepiness (EDS). As a consequence of hypoventilation or apnoea during sleep these patients have frequent arousal causing the EDS. These patients have significant apnoea which are both obstructive and central.

Myasthenia gravis is another disorder we studied and found sleep associated breathing affection being common. They often complain of waking up from sleep with shortness of breath in the early hours when the longest REM sleep periods occur especially if they omit their night dose of Pyridostigmine.

These neuromuscular disorders have been helped by assisted ventilation. Nasal Bilevel Positive Airway Pressure (BIPAP) system obviates the need for tracheotomy.

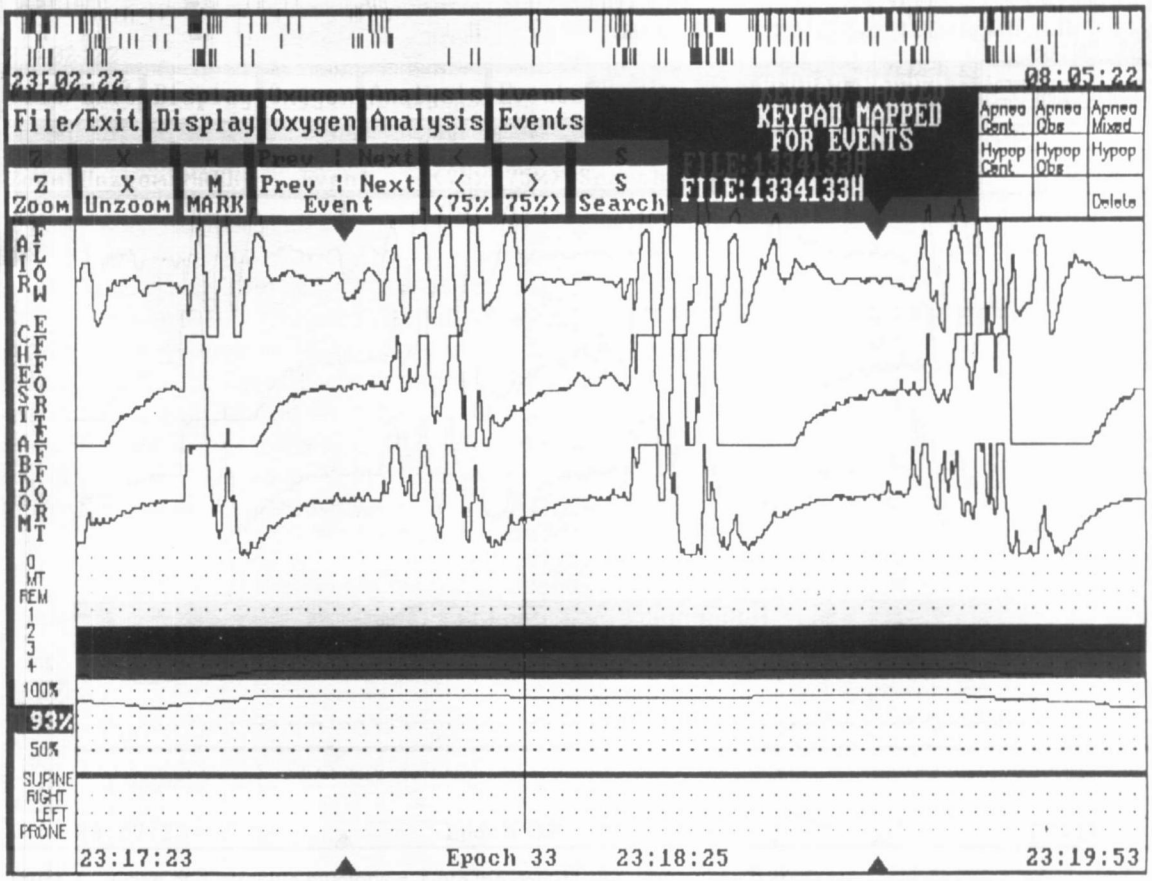


Figure 7. Case of dystrophia myotonica. Note the central apnoea in stage 2 sleep shown in one epoh of recording.

Periodic limb movement during sleep (PMS)[7] :- We are recognising this condition as a frequent cause of insomnia (17%) or Excess daytime sleepiness (11%) in patients. Stereotyped movements of the limbs occur periodically, predominantly in the legs. It is not myoclonic (though called nocturnal myoclonus) and is identical to the babinski response. Suppression of the descending inhibition on pyramidal function in suspected. It lasts 0.5 – 5 sec in duration and is shown on anterior tibial muscle EMG as a burst of muscle activity. These could be seen as a jerk followed by tonic contraction. Average interval between jerks is 20-40 secs. At least 5 bursts per hour (PMS index 5) is required for diagnosis. Brief awakening and arousal occur after the tibialis anterior burst (Fig 8). Differential diagnosis is sleep apnoea where leg movements occur after arousal. There is rhythmic extension of the big toe and dorsiflexion of ankle. There is also flexion of knee and hip.

Patient is unaware of this though arousal or wakening occurs. PMS occurs in NREM sleep specially in stage 1 and 2. PMS occurs in Restless leg Syndrome (RLS). This is a syndrome described by Ekbom in 1954. Irresistible leg movements accompained by creeping sensation deep in limbs, characterises RLS and affects at least 5% of general population.

The exact role of PMS in production of symptoms is not known. Treatment is clonazepam. This only suppresses arousal but not the leg movement. RLS may not occur in all cases of PMS. Both are idiopathic and benign except that they disrupt sleep.

REM sleep behaviour disorder[1] – This is characterised by intermittent absence of the expected atonia of REM sleep which allows the victim to 'act out' dream mentation. This can result in violence and injury. The dreaming husband would fight to defend his wife while actually striking her. The PSG shows a very characteristic pattern of absence of atonia during REM sleep associated with violent behaviour which correspond with dream

mentation (Fig 9). 2 Forms of RBD occur. An acute form with drug, alcohol withdrawal. The chronic form affects old people and a third of these have a peri locus ceruleus lesion. We studied this in patients with parkinsons disease and olivo ponto cerebellar degeneration. Wakeful dreaming has been considered a cause of vivid visual hallucinations associated with delerium with tremens. We studied patients with alcohol withdrawal and delerium tremens. Violent behaviour came on as he just fell asleep and REM breaking through into wake state. The polysomnograph at this time showed stage REM with tonic EMG and the Video showed violent behaviour.

Sleep in Narcolepsy[8]

Narcolepsy is a neurological disorder associated with symptoms of excess Sleepiness and emotionally induced weakness (Cataplexy). Cataplexy is REM sleep muscle atonia without the cortical manifestation of Sleep. Other REM sleep phenomena such as sleep paralysis and hypnogogic hallucinations can occur. It is one of the most common gene determined disorders of the central nervous system. About 98% of Caucasians and 100% of Japanese patients carry HLA DR2/DQ1 antigen which is the strongest HLA disease association known. Its prevalence in San Francisco is said to be 0.05 percent. However on a survey in Singapore we find the prevalence as only 2.5 per 500,000 population. This is because the diagnosis is often missed or the disease is as rare as in Israeli Jews who have low percent of HLA DR2 (3%) compared with Caucasians and Japanese (10-35%). The prevalence of Narcolepsy in Israel is only one in 500,000.

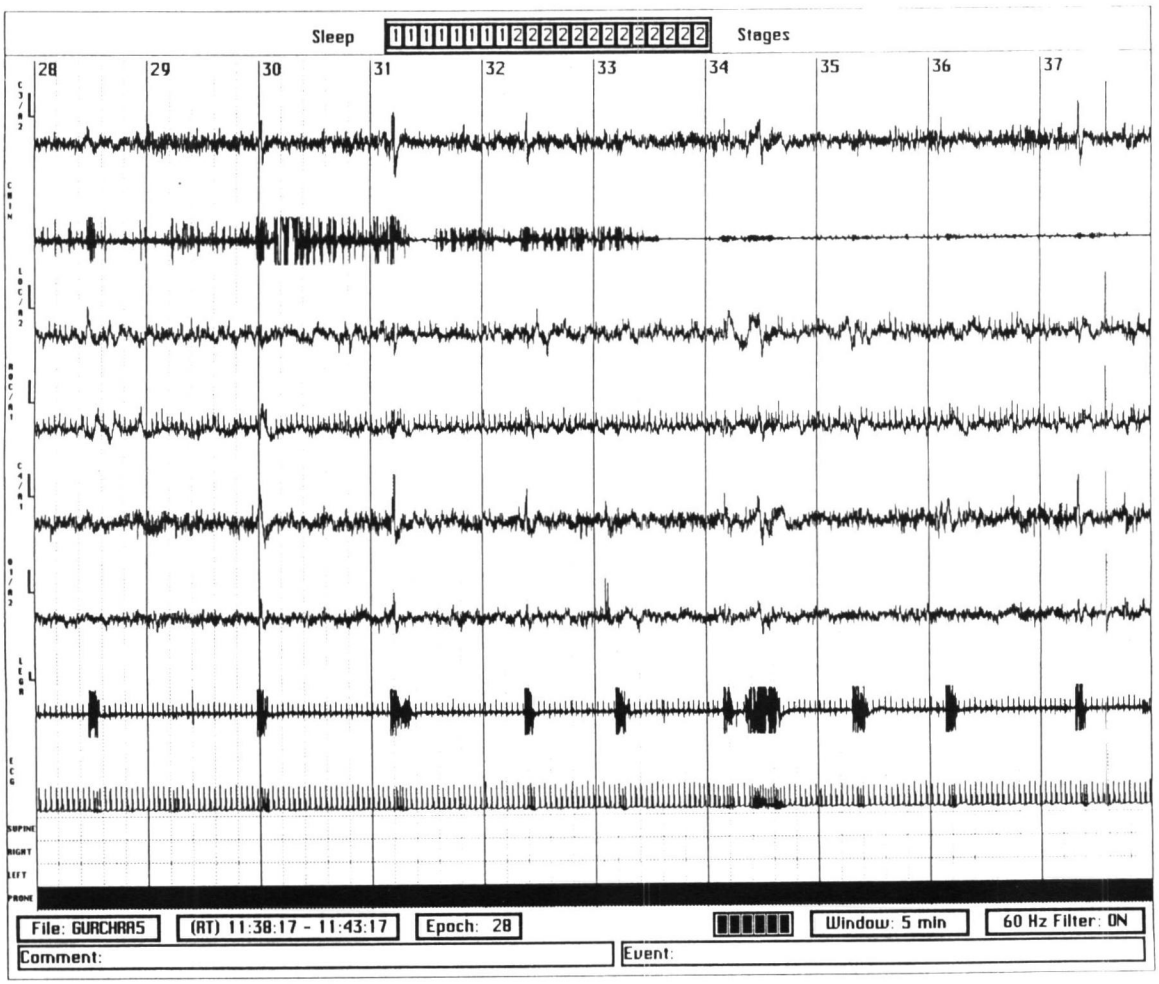


Figure 8. A 5 minute window of recording showing PMS. Tibialis anterior muscle recording on the seventh line shows periodic busts of EMG. This is associated with brief arousal shown as chin muscle activity on second line and tachycardia on ECG on the eighth line.

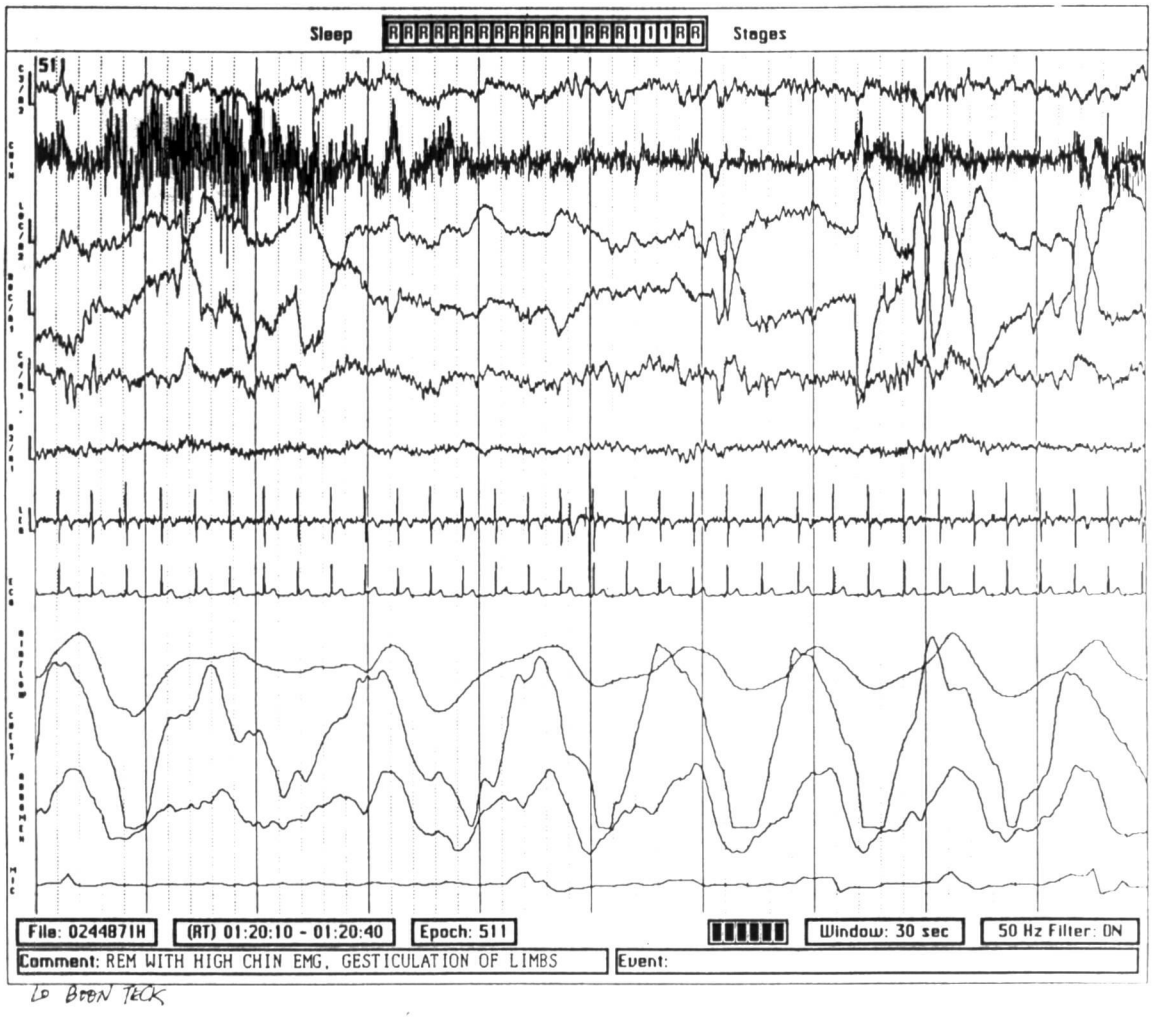


Figure 9. REM behavior disorder – One epoh (30 sec) of REM sleep (note rapid eye movements in third and fourth line) showing muscle activity on the chin muscle lead. Muscle activity in REM sleep is abnormal.

The polysomnogram shows characteristic features – Short latency to Sleep and Sleep onset REM (SOREM) within 20 mins. The most characteristic finding is on MSLT – short mean Sleep Latency to less than 5 min. 2 or more SOREM seen on MSLT.

Idiopathic Hypersomnia – Some patients with severe day time sleepiness but without REM sleep features and cataplexy would have this problem. Night sleep is long and day naps are also of several hours.

Parasomnias (Events around Sleep):

These are physiological and behavioural phenomena that occur during sleep. The behaviour results in injury or violence to self or others and excess sleepiness. The frequently encountered are night terrors, sleep walking, nocturnal seizure, REM behaviour disorders and Nightmares.

The Sleep wake pattern of humans follow a circadian rhythm. The industrial revolution in this century has brought on a steady erosion of circadian rhythm by shift workers, Jet Lag and space flight. Attempts to deal with jet-lag have concentrated on the sleep disturbance and the associated fatigue. The body clock has to adjust to the new time zone. The recent treatment of Jet Lag is melatonin. This reduces fatigue and improves sleep.

Legal aspects of sleep and alertness.

Sleep disorders and lack of alertness can cause various legal problems. The association between

daytime sleepiness and accidents is well known. It is a vexing question whether a person causing harm while sleep walking is criminally liable. It is becoming increasingly apparent that the impact of various drugs including sedatives, tranquillisers, hypnotics cause more daytime sedation than alcohol in terms of reduced psychomotor performance, thereby seriously affecting a persons ability to drive or operate heavy machinery. When a driver falls asleep at the wheel, the courts may convict him of a driving offence on the grounds that the driver should have pulled off the road when he started to feel drowsy. However these are circumstances in which sleep is entirely unpredicted. This occurs in Microsleep (or Narcolepsy).

Microsleeps

With tiredness or after sleep deprivation short microsleeps occur during period of wakefulness. These are short 1-10 second bursts of stage 1 sleep, with loss of alpha activity or stage 2 NREM sleep. These periods of subwakefulness occurs in normal people in the above circumstances (and also in Narcolepsy). The alteration of awareness of automatic behaviour is not perceived and these is amnesia for these events. Frequent automobile accident, driving on the wrong side of road neglecting traffic signals occurs typically. These attacks are difficult to distinguish from automatism associated with partial complex seizures, or absence seizures, transient global amnesia or simple day dreaming. The concept of microsleep is not well known among doctors and the public.

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