Brief Review

Beyond apnoea

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SUMMARY. Chronic sleep deprivation, resulting from either socio-occupational habits or disorders compromising sleep, is considered to be a major cause of social, occupational and personal dysfunction, but it is also one of the most common contributing factors to mortality and physical disability. With the exception of obstructive apnoea, which accounts for the greater part of all diagnostic and therapeutic procedures related to sleep disorders, the majority of disorders remain undetected and untreated. The coexistence of more than one sleep disorder in the same patient is not uncommon, especially in certain groups of patients, such as those with neuromuscular and neurodegenerative diseases. In these cases, partial diagnosis is equivalent to no diagnosis. The aim of this review is to present the most common sleep disorders, other than obstructive apnoea, which independently or in combination are responsible for the majority of complaints concerning chronic sleep deprivation.t.
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INTRODUCTION

The recognition of sleep disorders as one of the most common contributing factors to mortality and disability associated with the contemporary life style [1] has guided scientific research towards the investigation of the physiological and pathophysiological mechanisms governing the process of sleep and its disorders. Frequently, a so-called human error [2] occurs as a result of the disruption of the subject's normal nocturnal sleep, which ultimately results in chronic sleep deprivation and has serious consequences for that person's diurnal functional status.[3] Chronic sleep deprivation is characterized by the untimely onset of sleep during activities that require full alertness (e.g. driving). This drowsiness is combined with difficulties in concentration and the execution of mental tasks, and psychological and sexual disorders.[3] The most common cause of sleep derangement is obstructive apnoea syndrome, which is easily diagnosed based on its typical clinical and polysomnographic features. Obstructive apnoea can be treated successfully with the use of a continuous positive airway pressure (CPAP)

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device. However, patients with sleep apnoea who are receiving appropriate treatment with CPAP often continue to complain of sleepiness. In this case, two questions must be answered: a) can this treatment failure be attributed to technical issues associated with the CPAP device and its use, or b) is the patient suffering from another sleep disorder in addition to obstructive apnoea?

This review aims to approach the second question, covering the presentation, diagnostic evaluation and management of central sleep apnoea, restless leg syndrome (RLS), periodic limb movements during sleep, parasomnias during NREM and REM sleep stages and narcolepsy. These conditions all result in sleep derangement, and may coexist and interact with obstructive apnoea.

Central sleep apnoea syndrome

The central sleep apnoea syndrome is characterized by frequent episodes of central apnoea during sleep that cause hypoxia and arouse the patient, ultimately resulting in interruption and deprivation of refreshing sleep. Theoretically, the pathophysiology of the syndrome involves loss of neural signalling from the respiratory centres, resulting in lack of airflow and thoracic- abdominal movements (fig. 1, 2). Episodes of apnoea with similar features can also be caused by peripheral respiratory dysfunction (peripheral nerves-muscles).[4] In these conditions, the reduced respiratory movement and airflow are attributed to muscle weakness.

The main causes of brainstem respiratory centre dysfunction are cardiac failure,[5] use of central nervous system (CNS) suppressants (barbiturates, benzodiazepines, opioids),[6,7] brainstem lesions caused by ischaemic, demyelinative, traumatic or invasive processes,[4] and diffuse lesions in cerebral white matter.[8] Congenital central hypoventilation is a rarer cause.[9] The syndrome is characterized as idiopathic when a cause cannot be

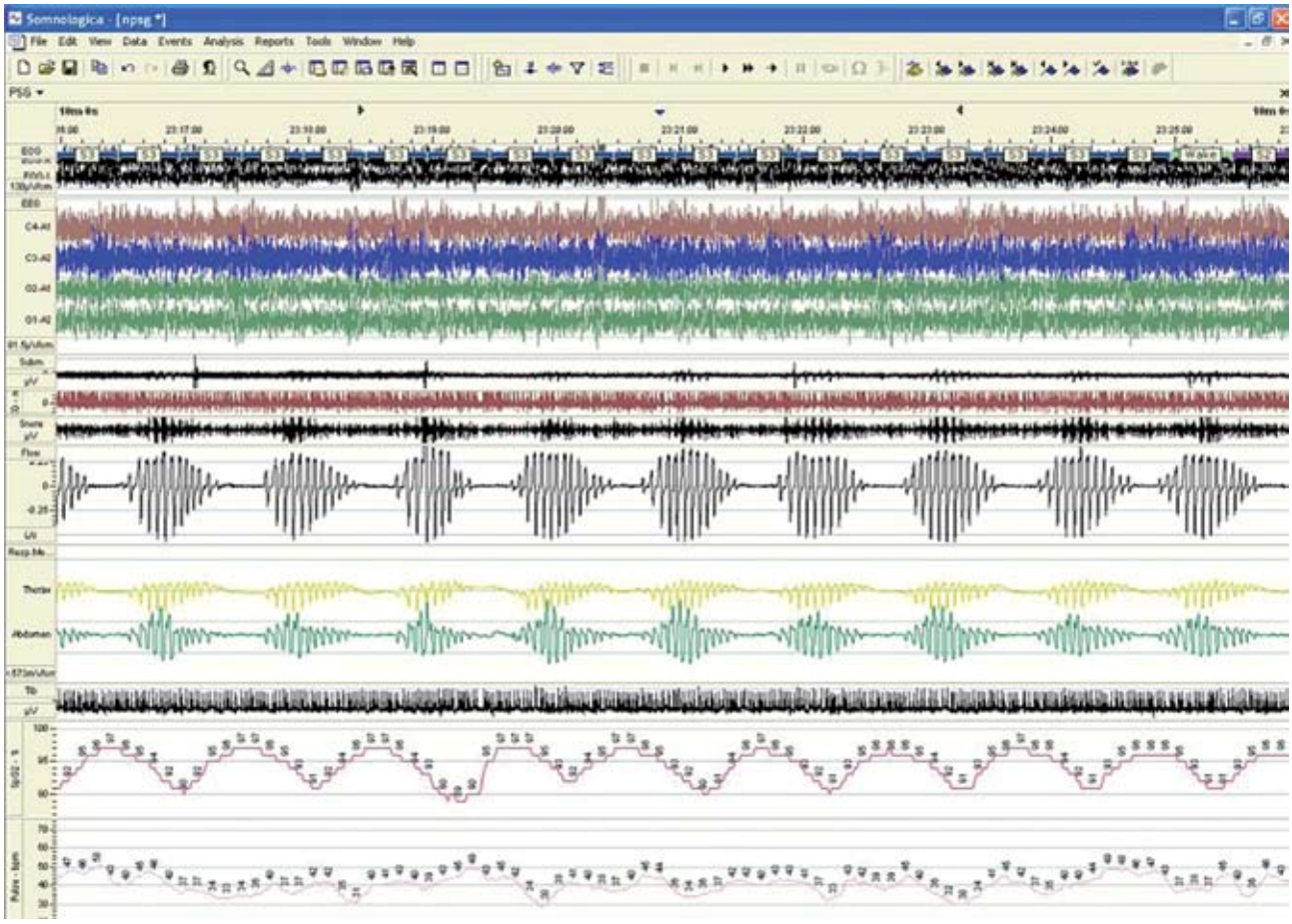

Figure 1. Cheyne Stokes respiration. Part of a polysomnographic recording lasting 10 minutes. The patient suffers from cardiac failure. *Sleep Study Centre, St. Thomas's Hospital, London*.

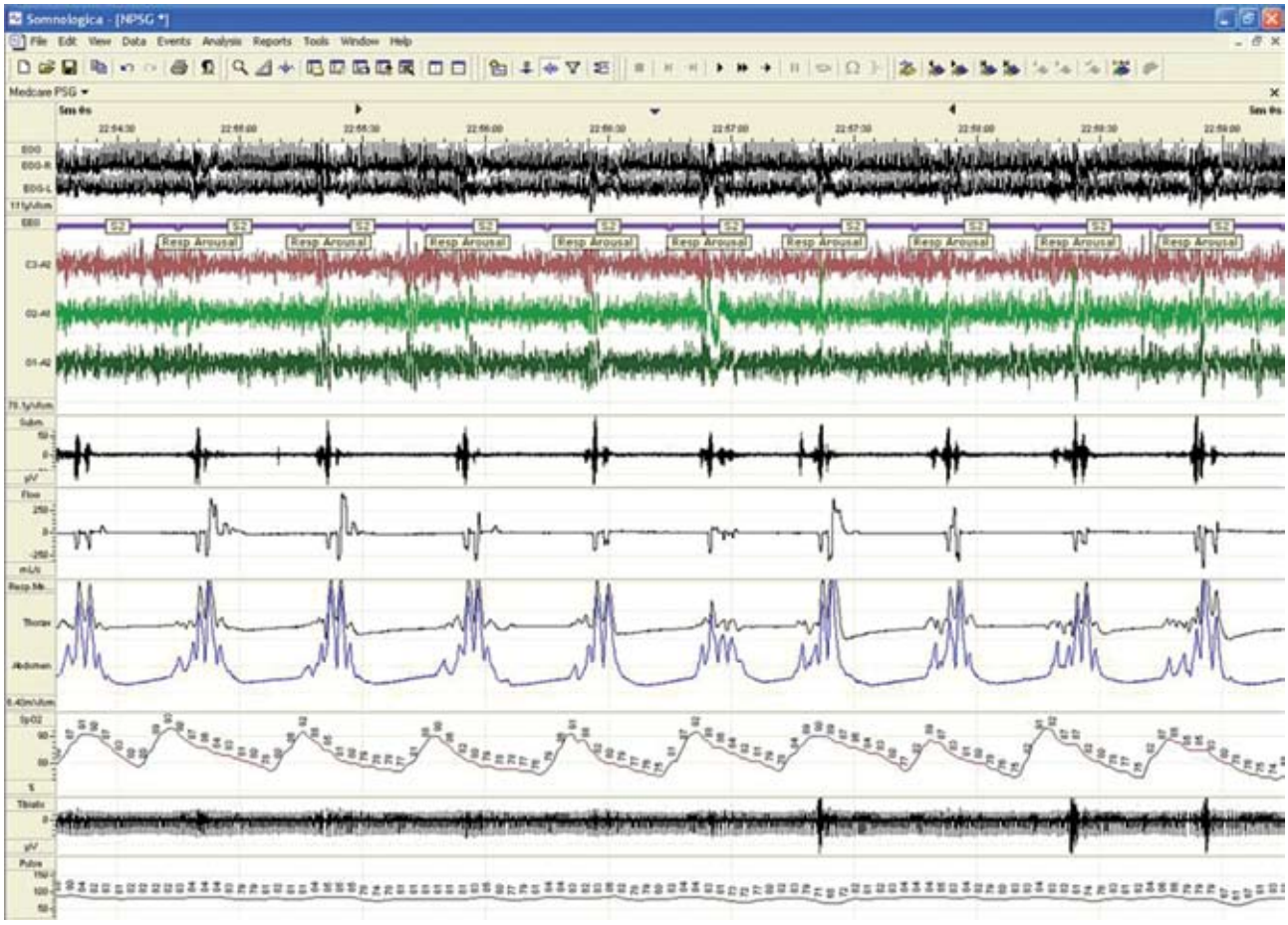

Figure 2. Periodic breathing. Part of a polysomnographic recording lasting 5 minutes. The patient presented with diurnal sleepiness and inability to complete uninterrupted sleep. History and laboratory investigations failed to reveal a primary cause for the central apnoea episodes. The patient was diagnosed with idiopathic central apnoea syndrome and was successfully treated with temazepam. *Sleep Study Centre, St. Thomas's Hospital, London.*

identified.[4] Causes of central apnoea due to peripheral dysfunction include a variety of neuromuscular diseases (motor neurone disease, polymyositis and post-polymyositis syndrome, myasthenia and the myopathies), kyphoscoliosis, the obesity-hypoventilation syndrome and autonomic nervous system diseases (diabetes mellitus,[10,11] autonomic neuropathies, neurodegenerative diseases).

Typical general symptoms of chronic sleep deprivation can be identified, as well as specific symptoms related to the primary cause. Diagnosis requires recognition of one of the three types of central apnoea during polysomnography:

a. Cheyne-Stokes respiration, which is defined as repetitive episodes of central apnoea with progressive onset and regression, forming a typical wave pattern (Figure 1). Approximately 37% of patients with cardiac failure with an ejection fraction of < 45% produce Cheyne-Stokes respiration; rarer causes are cerebrovascular disease and other brainstem lesions;
b. Regular periodic respiration, consisting of intermittent episodes of apnoea with rapid onset and regression (Figure 2). This type is more common in secondary central apnoea, but can also appear in idiopathic apnoea;
c. Sleep hypoventilation (Figure 3), which is characterized by hypercapnia and prolonged episodes of desaturation combined with features of central apnoea. It is prevalent in neuromuscular disorders, congenital central hypoventilation syndrome and obesity-hypoventilation syndrome. Hypoventilation tends

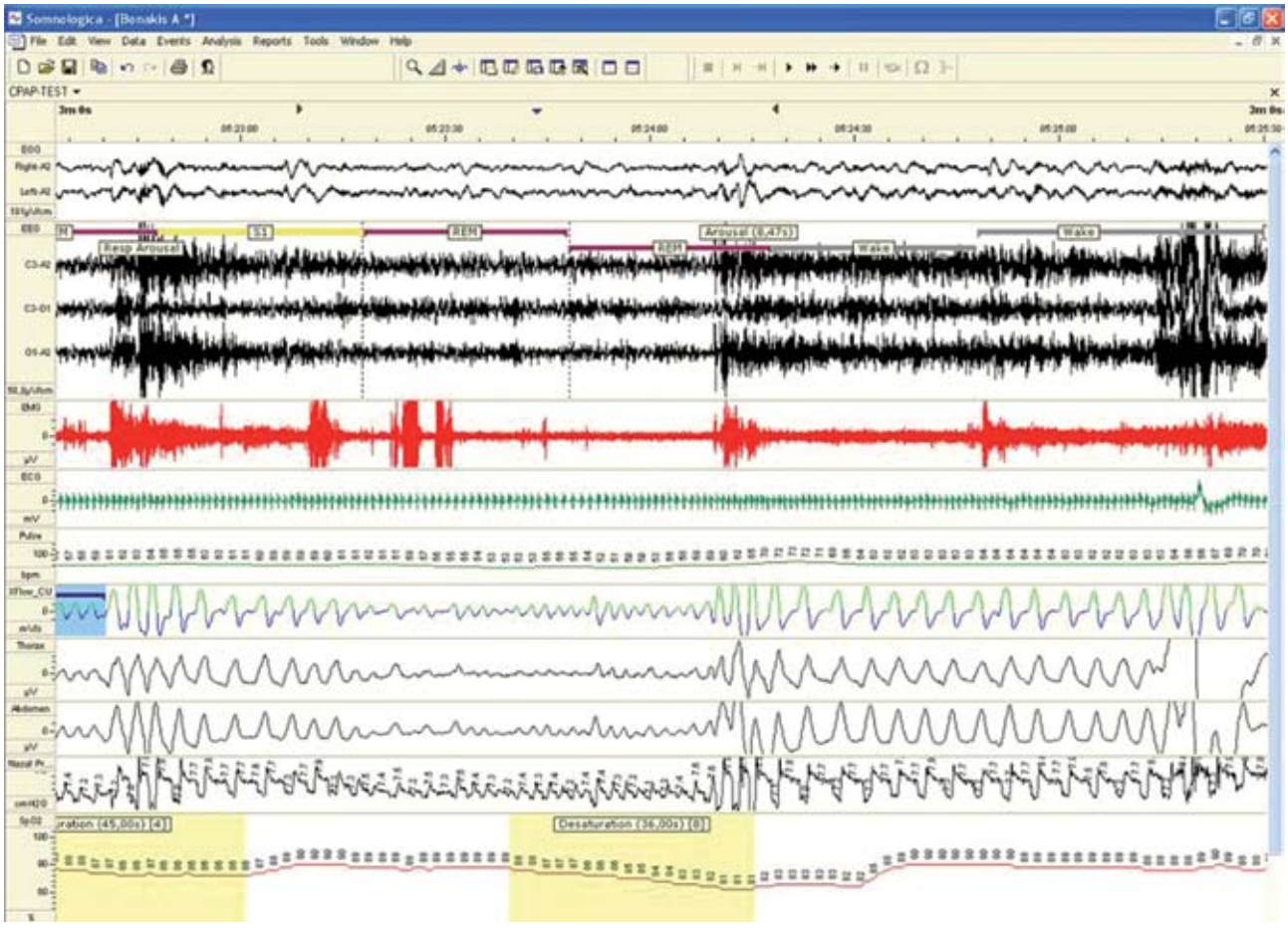

Figure 3. Hypoventilation during sleep. Part of a polysomnographic recording lasting 3 minutes. The patient suffers from myotonic dystrophy. With the onset of REM stage and despite the use of CPAP, prolonged episodes of central apnoea occur that arouse the patient. *Sleep Study Centre, Evangelismos Hospital, Athens*.

to deteriorate during the REM stage in neuromuscular disorders, whereas it is far more pronounced during the NREM stage in congenital central hypoventilation and obesity-hypoventilation syndrome.[4]

Central apnoeas usually occur with the onset of sleep, between sleep stages and after an EEG arousal.[12] In patients predisposed to developing central apnoeas, the presence of an additional factor causing frequent arousals (e.g. periodic limb movements, obstructive apnoea, upper airway resistance syndrome, narcolepsy,[13] painful disorders, etc.) can increase significantly the number of apnoeas.[4,14]

The treatment depends on the cause and type of apnoea as well as its interaction with other sleeping disorders. Central apnoea syndrome due to cardiac failure is initially managed by improvement of the blood supply by pharmacological means and, if further reduction of apnoeic events is needed, non-invasive ventilation is suggested (especially the use of adaptive servo-ventilation devices).[15,16] Management of periodic respiration also involves treatment of concomitant sleeping disorders that can cause repetitive arousals and shifts in sleep stages. If apnoeas persist, administration of benzodiazepines can help preserve deep sleep and increase the stimulation threshold. Alternative means of treatment are theophylline, acetazolamide, oxygen administration or CPAP/non-invasive mechanical ventilation.[15] The management of sleep hypoventilation consists entirely of non-invasive ventilation.

The following should be emphasized:

1. Diagnosis and treatment of other disorders causing frequent arousals (such as periodic limb movements) can significantly reduce the number of apnoeas and ensure undisturbed sleep in patients with central

apnoeas and sleep derangement (Figure 4).

2. In obstructive apnoea, the appearance of central apnoeic episodes is almost certain. When the number of episodes is significantly high, this poses the problem of differential diagnosis. Typically, central apnoea syndrome is diagnosed when ≥ 50% of the episodes are scored as central [4] ; however, this is an arbitrary threshold.
3. Events of periodic respiration occur mostly during stages 1 and 2 and are significantly reduced or disappear in stages 3 and 4 of NREM sleep.

Restless leg syndrome

RLS is characterized by an unpleasant feeling in the limbs, but mostly the lower limbs, when the patient is in the resting position. This feeling may be described as pain, burning or numbness and is accompanied by an overwhelming desire to move the legs. The symptoms may appear at any time during the day, but are usually exaggerated at night, as they are affected by the circadian rhythm,[17] causing difficulty in the onset of sleep. The limb movements persist during sleep, resulting in frequent arousals, chronic insomnia and diurnal sleepiness.

Pathophysiologically, RLS has been associated with deficiency of iron and dopamine .[18] It has been suggested that dopamine plays a significant role, as the administration of dopamine or dopamine receptor agonists has produced impressive results. Iron depletion has been associated with RLS because of its role in dopamine production.[18] The most common causes of iron deficiency are nutritional disorders, chronic blood loss, pregnancy, dialysis and use of antidepressants (serotoninergic, tricyclic antidepressants) or neuroleptic agents that bind to dopamine receptors. In the absence of a detectable primary cause, RLS is termed idiopathic. RLS is an inheritable condition in a significant percentage of cases.[19] The syndrome is more prevalent in certain groups of patients,

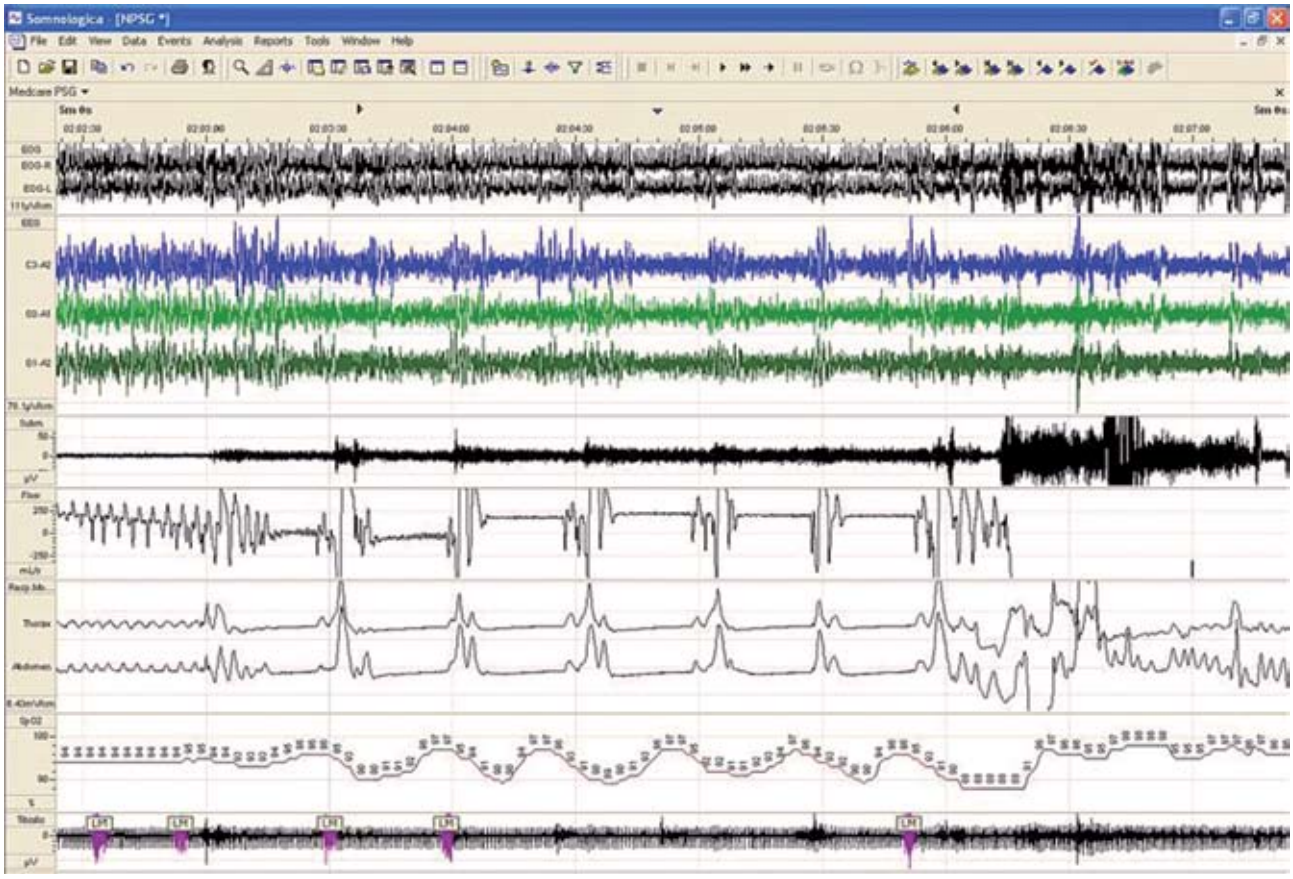

Figure 4. Part of a polysomnographic recording lasting 5 minutes in a patient with daytime sleepiness. The apnoea-hypopnoea index is 44/hour and all recorded episodes are scored as central. A very high index of periodic limb movements was also observed (90/hour). The patient was diagnosed with restless leg syndrome and successful management also minimized central apnoeic episodes. *Sleep Study Centre, Evangelismos Hospital, Athens*.

such as those with Parkinson's disease or attention deficit disorder.[20]

The diagnosis of RLS is clinical and is based on the association of symptoms with akinesia, nocturnal exaggeration and a positive family history. In clinical practice, many patients present with atypical symptoms and differential diagnosis must be made from other disorders with similar presentation (e.g. numbness and cramps of the lower limbs in peripheral neuromuscular disorders, lower limb venous insufficiency, musculoskeletal syndromes, neuroleptic akathisia, etc.) with use of polysomnography. Periodic limb movements, which accompany the syndrome at a rate of 85%, can be identified polysomnographically.[21] Unfortunately, periodic limb movements are sometimes absent and the polysomnography recordings may reveal no pathological findings. In these cases, actigraphy for one or two weeks with application of the actigraph on the tibia can provide useful information regarding the presence of movements and the severity of relative insomnia.[22] Therapeutically, the iron stores must be replenished, and administration of dopamine or dopamine agonists can be effective. Alternative medication is clonazepam or gabapentin.

It is reported that 2-4.5% of patients with obstructive apnoea also suffer from RLS.[23] This combination is more prevalent in the older age group or in specific groups of patients, such as patients with Parkinson's disease.

The following should be emphasized:

1. RLS should always be suspected in patients with obstructive apnoea and diurnal sleepiness that persist despite correct use of CPAP. These patients should be re-evaluated frequently with a polysomnographic study on CPAP.
2. Obstructive apnoea syndrome is associated with a high index of periodic limb movements on polysomnography. Pending the diagnosis of RLS, obstructive apnoea should be treated and the patient re-evaluated for recessive apnoea.

Periodic limb movement disorder

This disorder is characterized by a high index of periodic limb movements (PLMI) during sleep and diurnal sleepiness that cannot be attributed to any other cause.[24] The patient's history usually reveals increased motor activity during sleep or troubled sleep. Periodic leg movements frequently accompany a variety of conditions, including use of certain medications, obstructive apnoea, narcolepsy, neurodegenerative disorders and hyperkinetic syndrome of childhood, etc., without presence of clinical signs of restless leg syndrome during the alert phase. This suggests that the two syndromes are not identical.

In obstructive apnoea with a high PLMI, it has been reported that the PLMI can be either decreased or increased with the use of CPAP.[25] This is probably because uninterrupted sleep allows periodic limb movements to occur in some patients, whereas in others, limb movements related to arousals may disappear.

The diagnosis is confirmed by polysomnography, which reveals a PLMI of > 5 series of movements per hour. Management is similar to that of RLS.

The following should be emphasized:

1. Periodic limb movement syndrome is not the same as RLS, although the latter can be accompanied by periodic limb movements during sleep.
2. Periodic limb movements can be caused by respiratory disorders. The primary respiratory disorder should be treated initially and if sleepiness persists, then the patient must be re-evaluated in order to assess the contribution of periodic limb movements to the disruption of sleep.

Parasomnias

Parasomnias are characterized by abnormal behaviour during sleep, which can consist of voluntary limb movements, events involving fear, speech and even the performance of complex actions, such as driving, cooking, wandering, etc. A division is made into parasomnias occurring during the NREM stage (sleepwalking, sleeping tremor, etc), those during the REM stage (behaviour disorder during REM sleep, nightmares) and those occurring in both stages.[26] These conditions are very stressful not only for the patient but also for the family environment.

NREM parasomnias are defined as complex behaviour consisting of leaving the bed and performing actions (getting dressed, cooking, driving, etc). The patient usually remains asleep and occasionally extreme behaviour has resulted in injury or death of the patient or others. Characteristically, there is no recollection of these events in the following morning. Parasomnias are caused by difficulty in arousal from deep sleep, allowing the sleepwalker to perform actions without the ability to record them, due to slow EEG activity of the brain cortex. This feature is genetically regulated, as suggested by the hereditary component in most patients. Differential diagnosis of NREM parasomnias includes nocturnal frontal lobe epilepsy. Polysomnography is not essential for diagnosing

NREM parasomnias; however it can be helpful by recording sudden automatic arousals from deep sleep, although this is a non-specific finding. The major contribution of polysomnography in parasomnias is the identification of underlying sleep disorders that can cause these arousals. In people predisposed to NREM parasomnias, stimuli that cause arousal from deep sleep increase the possibility of developing parasomnias. Therefore, insurance of a good sleeping environment without noise and light combined with the diagnosis and treatment of possible coexisting sleeping disorders (snoring, obstructive apnoea, RLS, etc) are essential for the treatment of NREM parasomnias.[28]

Behavioural disorder during REM sleep is characterized by dream enactment behaviour. The dream content is usually a nightmare and the patient exhibits defensive or aggressive behaviour causing self-injury or injury of a bed partner. Arousal is easy and usually there is recollection of the dream. The main causes of the disorder are medication and central nervous system diseases affecting the brainstem.[28] Polysomnography is not considered necessary for the diagnosis, but it can be helpful in atypical cases, when increased muscular tone is recorded in the chin EEG during the REM stage. Serious obstructive apnoea can cause similar behaviour in the REM stage, accompanied by limb jerks and infliction of injury to self or partner.[29] Moreover, obstructive apnoea and REM sleep behaviour disorder often coexist in patients with Parkinson's disease, multiple system atrophy and other nervous system disorders. These conditions require polysomnography to establish the diagnosis and treatment. The use of CPAP can improve sleep behaviour disorder,[30] whereas administration of clonazepam (the medication of choice) may worsen apnoea. For these reasons, complex disorders are best treated by titrating the pressure of CPAP at the sleep centre after the administration of clonazepam. An alternative treatment of REM sleep behaviour disorder consists of melatonin,[31] which has shown satisfactory results without worsening the apnoeas.

The following should be emphasized:

1. Sleepwalkers are advised to avoid stimuli that can cause arousals, because partial arousal can lead to somnambulism. Administration of suppressants (benzodiazepines) is indicated when injurious behaviour is exhibited.
2. The sleepwalker must be cared for and gently escorted back to bed. Efforts to arouse usually fail and may lead to aggressive behaviour.
3. Before diagnosing REM behaviour disorder in patients with serious obstructive apnoea (apnoeic index > 30/hour), REM stage muscular tone must be evaluated and any respiratory disorder must be managed.
4. Pharamacological treatment of REM behaviour disorder consists of clonazepam, which, however can worsen apnoea during sleep.
5. Melatonin can be administered instead of clonazepam in patients with a combination of REM behaviour disorder and obstructive apnoea.

Narcolepsy

Narcolepsy is a clinical syndrome characterized by diurnal sleepiness described as attacks of sleep, which are typically irresistible and very refreshing. Other clinical manifestations are: a) cataplexy, which comprises sudden loss of muscular tone in various muscle groups (mostly the lower limb and facial muscles) leading to falls without concomitant loss of consciousness or injury, b) sleep paralysis, e.g. events of complete inability to move (stand, speak, or even blink) following arousal, and c) hypnagogic hallucinations, which are optical illusions consisting of vivid oneiric images with the onset of sleep or in wakefulness. These symptoms are caused by inappropriate appearance of features of REM sleep (oneiric state, loss of muscular tone), most often with the onset of sleep. Narcolepsy can be defined as either secondary to anatomical lesions affecting the subthalamus, or idiopathic. Idiopathic narcolepsy is caused by autoimmune destruction of the subthalamic cells responsible for the production of hypocretin-1.[32] The international classification of sleep disorders[33] discriminates between two similar syndromes, narcolepsy-cataplexy and narcolepsy without cataplexy. This discrimination is considered essential as the presence or absence of cataplexy has been correlated with essential biochemical and genetic differences. Patients with narcolepsy-cataplexy have low levels or complete absence of hypocretin-1 in the cerebrospinal fluid (CSF), at a very high rate, and are also positive for HLA DQB1 0602 haplotype.[34] The Diagnosis of narcolepsy is based on the history (presence of cataplexy attacks without concomitant mental disorder suffices to establish the diagnosis) and confirmed by multiple sleep latency test (MSLT), testing for HLA DQB1 0602 haplotype and measurement of hypocretin-1 in the CSF. Of these, MSLT is considered the most practicable for the diagnosis. It requires the polysomnography equipment and involves four efforts to sleep during daytime with duration of 20 minutes each. Two primary parameters are studied: a)

median sleep latency in all efforts, and b) presence of REM period in all efforts. Median sleep latency < 8 minutes and > 2 REM periods in the total of four efforts appear in 71% of patients with narcolepsy-cataplexy and in 91% of patients with narcolepsy without cataplexy. However, similar findings are observed in 6% of patients with breathing disorders during sleep caused by disturbance of REM stage from apnoeic episodes. Therefore, MSLT should be performed in the day immediately after a standard polysomnographic study, which recorded at least 6 hours of sleep with REM periods, and provided that the patient reports sufficient nocturnal sleep for at least two weeks prior to the test. Conditions causing chronic sleep deprivation and especially REM sleep deprivation can present with the symptomatology of narcolepsy, but without cataplexy attacks. Cataplexy exclusively accompanies narcolepsy and CNS disorders with mental retardation.[35]

The management of narcolepsy is both behavioural and pharmacological. Patients need to follow a precise sleeping schedule. If possible, they should take at least 2-3 one-hour naps during the day, at specific hours. Persistent diurnal sleepiness can be managed with amphetamine or modanafil administration and cataplexy with tricyclic and serotoninergic antidepressants or sodium oxybate administration. Another acceptable method in the management of narcolepsy is CPAP, due to the observed high rates of obstructive apnoea in these patients,[13] possibly attributed to the increased prevalence of obesity.[36]

The following should be emphasized:

1. Patients with severe obstructive apnoea may present with symptomatology similar to narcolepsy lacking REM periods.
2. A very high percentage of narcoleptic patients are obese; consequently they have high rates of obstructive apnoea. Therefore, it is crucial that obstructive apnoea is treated in these patients, as it can considerably contribute to daytime sleepiness.

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