Review Article

Diagnosis of circadian rhythm sleep disorders*

Diagnóstico dos transtornos do sono relacionados ao ritmo circadiano

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Abstract

Insomnia and excessive sleepiness are common in the investigation of sleep-disordered breathing. Circadian rhythm sleep disorders are perhaps the most often overlooked conditions in the differential diagnosis of these symptoms. Circadian rhythm sleep disorders manifest as misalignment between the sleep period and the physical/social 24-h environmental cycle. The two most prevalent circadian rhythm sleep disorders are delayed sleep phase (common in adolescents) and advanced sleep phase (common in the elderly), situations in which the sleep period is displaced to a later or earlier time, respectively. It is important to keep these two disorders in mind, since they can be confused with insomnia and excessive sleepiness. However, there are nine possible diagnoses, and all nine are of clinical interest. Since light is the principal cue used in synchronizing the biological clock, blind individuals and night-shift/swing-shift workers are more prone to develop circadian rhythm sleep disorders. In this article, the new international classification of circadian rhythm sleep disorders is reviewed.

Keywords: Circadian rhythm; Sleep disorders; Sleep initiation and maintenance disorders; Sleep stages; Sleep apnea syndromes.

Resumo

Queixas de insônia e sonolência excessiva são comuns na investigação dos distúrbios respiratórios do sono; os transtornos do sono relacionados ao ritmo circadiano talvez sejam as causas mais freqüentemente esquecidas no diagnóstico diferencial destes sintomas. Estes transtornos se manifestam por desalinhamento entre o período do sono e o ambiente físico e social de 24 h. Os dois transtornos do sono relacionados ao ritmo circadiano mais prevalentes são o de fase atrasada (comum em adolescentes) e avançada do sono (comum em idosos), situações nas quais o período de sono se desloca para mais tarde e mais cedo, respectivamente. As possíveis confusões com insônia e sonolência excessiva tornam importante ter sempre em mente estes transtornos. Entretanto, há nove possíveis diagnósticos, e todos são de interesse clínico. Como a luz é o principal sinal para sincronizar os relógios biológicos, pessoas cegas e trabalhadores em turnos e noturno são os mais propensos a desenvolver transtornos do sono relacionados ao ritmo circadiano. Neste artigo, revisa-se a nova classificação internacional dos transtornos do sono relacionados ao ritmo circadiano.

Descritores: Ritmo circadiano; Transtornos do sono; Distúrbios do início e da manutenção do sono; Fases do sono; Síndromes da apnéia do sono.

Introduction

Insomnia and drowsiness are complex symptoms that are difficult to quantify due to the various dimensions that each symptom presents. Insomnia, for example, can cause significant suffering and functional damage. However, if quantified in terms of number of sleep hours lost, it can be trivial. Likewise, drowsiness can go unnoticed or be denied by the patient, while it causes great concern to family members who observe naps in inappropriate situations, even behind the wheel of a motor vehicle.

The most common cause of drowsiness among individuals who seek medical assistance due to sleep disorders is obstructive sleep apnea-hypopnea syndrome (OSAHS). Apnea and hypopnea are episodes of sleep-disordered breathing of more than 10 s in duration that cause hypoxemia during sleep and do not appear during waking. The diagnosis of OSAHS is made based on the occurrence of sleep-disordered symptoms such as drowsiness or insomnia, accompanied by five or more episodes of apnea or hypopnea

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per hour of sleep.[1,2] Typically, OSAHS causes drowsiness, increasing the risk of accidents, especially traffic accidents. When OSAHS involves professional drivers, the risk increases,[3] leading to the death of passengers and bystanders.[4] The clinical importance of OSAHS has increased so greatly that the study of sleep-disordered breathing has become mandatory for a residency in pulmonary disease. Due to the epidemiological relevance of OSAHS, there are currently more pulmonologists than neurologists or psychiatrists who specialize in sleep disorders. The treatment of OSAHS results in better quality of life and reduced mortality rates. In order to institute treatment, a hypothetical diagnosis should be followed by investigation and differential diagnosis.

Among the causes of insomnia and drowsiness that are unrelated to respiratory diseases, the most neglected causes might be those related to circadian rhythm sleep disorders (CRSDs). These disorders manifest as misalignment between the sleep period and the physical/social 24-h environmental cycle, related to alterations in internal timing mechanisms. These disorders present two typical patterns, which are principally seen in the adolescent and in the elderly. The complaint that adolescents report can mimic insomnia when they lie down at regular times and it takes them hours to fall asleep. However, it can also mimic drowsiness when they cannot get up in the morning. The elderly can appear to have drowsiness when they fall asleep at 8 pm, while watching television, but they can also seem to have insomnia when they wake up in the middle of the night and cannot go back to sleep (Figure 1). These cases of pseudo-insomnia or drowsiness are actually the most common models of CRSD, with serious consequences to the quality of life of the individual. Therefore, they should always be considered in the differential diagnosis of OSAHS.

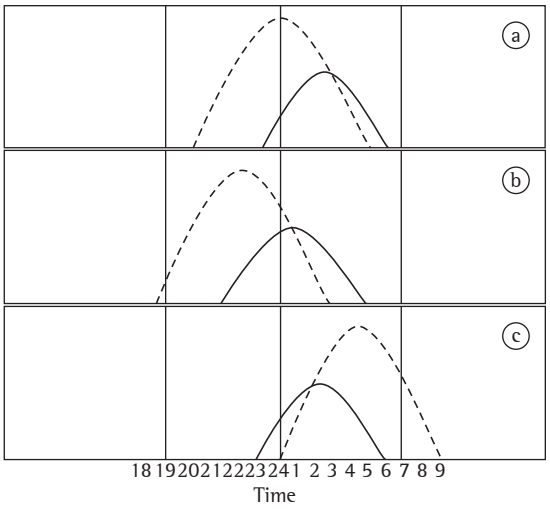

Figure 1 - Diagrams representing melatonin secretion (dashed line) and the sleep period (solid line) in normal individuals (a), individuals with advanced sleep phase (b) and individuals with delayed sleep phase (c). In normal individuals, melatonin secretion begins early in the evening and peaks around midnight, when the person lies down and falls asleep without difficulty; in the morning, the effect of melatonin has worn off, and the person arises without any drowsiness. In the advanced phase, melatonin peaks at 10 pm, causing irresistible drowsiness, and its effect wears off by 4 am, resulting in early awakening. In the delayed phase, if the individual tries to go to bed at 11 pm, initiating sleep will be difficult, since melatonin levels have not yet begun to increase; when getting up in the morning, melatonin will be near peak and drowsiness will be maximal, causing symptoms that can be confused with sleep-disordered breathing.

Sleep and timing mechanisms

Practically all living forms have timing mechanisms, or oscillators, which improve their chances of survival on a planet marked by light/dark cycles and seasons. For plants, the presence or absence of sun represents the furnishing of energy or the need to save energy. For animals, in addition to their 'spatial niche', a 'temporal niche' is necessary, a time when they are less exposed to predators and stand a greater chance of obtaining food. These temporal niches distinguish, for example, diurnal species from nocturnal species, as in the case of the thrush and the owl, respectively. In addition to diurnal cycles, there is the adaptation to seasons, which is essential to survival. Seasonal behavior is also controlled by internal calendars.[5]

Homo sapiens are diurnal, adapted to perform their activities during the light phase of the light/dark cycle and rest during the dark phase. The development of our visual system and our dependence on luminous information characterize us as a diurnal species.[6] The principal sleep period in our species is therefore during the dark phase. However, there can be other moments of rest over the course

of the day. The system that controls sleep-related behaviors is complex[7] and comprises various elements,[8] comparable to an orchestra.[9] The center that conducts the concert of the chronobiology of the mammals is the suprachiasmatic nucleus (SCN) of the hypothalamus.[10] Located next to the optic nerve, this area of the hypothalamus receives connections from the retina that inform the system of the existence of light. Melatonin[11] is secreted by the pineal gland, according to the stimulus of the SCN in the absence of light, translating the photic information into chemical stimulus to all cells. Exposure to light interacts with the SCN and can alter biological clock cycles. Intense light late in the afternoon turns the biological clock back. Intense light early in the morning moves the biological clock forward.[12] Regular repetition of nocturnal sleep episodes characterizes the so-called sleep-wake cycle. In addition to sleep, all functions of the nervous system present oscillations. The various components of human performance are erroneously considered stable phenomena. Evidence derived from laboratory studies, under controlled conditions and through manipulations of the sleep-wake cycle, demonstrates that performance is strongly affected by cyclic phenomena.[13] Living organisms are not machines that, once switched on, function uninterruptedly and with minimal oscillations.[14] Physical and mental oscillations in human beings are of relevant magnitude and high risk.[15] Fatal accidents represent the gloomiest side of drop in performance associated with circadian rhythms. The cycles that involve sleep and the processes that control it suffer disturbances of clinical interest,[16,17] which will be reviewed in this article.

As any biological system, oscillators responsible for the regularity of the sleep-wake cycle are subject to mutations,[18] as in the case of familial syndrome of advanced sleep phase, a dominant autosomal condition characterized by early sleep times and awakenings in the middle of the night. In addition to genetic aspects, there are chronobiological disorders secondary to various factors, such as: aging[19]; stress[20]; chronotype (morning or evening)[21]; and organic diseases.[22]

Despite the relative flexibility of sleeping and waking up time, human beings tend to maintain 24-h sleep-wake cycles. Deviations from this regularity typically occur on weekends, on vacations and during time zone changes. However, there are alterations of this cycle that go beyond the limits of normality. Such alterations primarily occur under chronic conditions such as those seen in night-shift/swing-shift workers. These alterations are identified as secondary CRSDs and merit specific treatment following correct diagnosis.

The diagnosis of sleep disorders is approached in several classifications. However, the most consistent international effort is that of medical societies dedicated to sleep disorders. The second version of the International Classification of Sleep Disorders (ICSD)[23] includes two new CRSDs that are of clinical interest, bringing the total number of possible diagnoses to nine (Table 1).

A diagnosis of CRSD can be made under certain conditions. First, the disorder must be accompanied by insomnia, excessive sleepiness or both, with social/occupational impairment or jeopardizing other areas. Second, the pattern of the disorder should be persistent or recurrent. Finally, the cause should be either an alteration in the timing mechanism or the lack of synchronization between the endogenous circadian rhythm and exogenous factors that affect the hour or the duration of sleep. These considerations are important since the sleep-wake cycle usually presents some variability, which also makes it possible to adapt to changes of habit on weekends.

Having met these general criteria, we should look for specific diagnoses such as those reviewed below.

Chart 1 - Classification of circadian rhythm sleep disorders.

Primary disorders
1) Delayed sleep phase
2) Advanced sleep phase
3) Sleep-wake cycle irregular pattern
4) Non-24-h sleep-wake cycle
Secondary disorders
5) Jet lag
6) CRSD secondary to work at irregular hours
7) CRSD secondary to diseases
8) CRSD secondary to the use of drugs or medications
Other
9) Other CRSDs

CRSD: circadian rhythm sleep disorder.

Circadian rhythm sleep disorders

Delayed sleep phase syndrome

Delayed sleep phase syndrome is characterized by late sleeping and waking, on most nights, usually with a delay of more than 2 h in relation to conventional or socially acceptable times. The patient has difficulty in initiating sleep and prefers to wake up later. When allowed to follow their preferred schedule, their circadian rhythm is chronically and persistently delayed, damaging their social life. Except for the delayed sleep schedule, their sleep is normal.

Family history can be present in up to 40% of the individuals with delayed phase. The prevalence in the general population is 7 to 16%. It is more common among adolescents and young adults, the prevalence being highest in individuals of approximately 20 years of age.[24,25] It is estimated that 10% of all patients with chronic insomnia who seek help in sleep clinics suffer from delayed phase syndrome.

The exact mechanism of the development of delayed phase syndrome is unknown. Genetic factors, such as polymorphism in the timing mechanism, principally of the *hPer3* gene, are associated with this syndrome. Environmental factors, including decreased morning light exposure, excessive light exposure late in the afternoon and late hours for television and video-games can exacerbate phase delay. Changes in work shifts and trips involving time zone changes can precipitate this disorder.

Chart 2 - Sleep hygiene measures for patients with circadian rhythm sleep disorders.

Respect the biological clock
Maintain regular hours for sleeping and getting up, using an alarm clock
Avoid variations of over 2 h in getting up time on weekends
Avoid staying in bed for over 7.5 h, including naps
Exercise at least 6 h before sleeping
Avoid exciting or emotionally disturbing activities near bed time
Avoid activities that demand a high level of concentration immediately before going to bed
Avoid mental activities such as thinking, planning, or recollecting in bed
Precautions regarding drugs, habits and environment
Prior to sleeping, avoid products that contain alcohol, tobacco, caffeine or any substance which acts on the central nervous system
Ensure that the bed is comfortable, that the mattress and sheets are of good quality, and that the covers are appropriate for the temperature
Ensure that the bedroom is dark and quiet, with an average temperature of 24°C (ranging from 17 to 27 °C)

Treatment

In all CRSDs, it is fundamental to supervise the adequate use of sleep hygiene measures (Table 2). Although these measures seem obvious, many patients totally ignore them, thereby making treatment impracticable, due to ingrained behaviors, such as ingesting high doses of caffeine at night. A simple way of treating delayed sleep phase is to further delay sleep initiation, at a rate of 2 to 3 h every 2 days, until the desired time of sleep period is achieved, ideally from 11:30 pm to 7 am. This method can be well accepted because it is easier to prolong wakefulness than to anticipate sleep. However, in practice, the need for rigorous compliance with the regimen and inconvenient intermediate hours compromise treatment efficiency. Intense light applied at the desired waking up time for 1 or 2 h readjusts the biological clock in a few days but also has practical limitations. Melatonin at a dose of 0.3 to 3 mg late in the afternoon contributes to advancing the sleep phase.

Advanced sleep phase syndrome

Advanced sleep phase syndrome is characterized by early sleeping and waking, on most nights, usually several hours before conventional or socially acceptable times.

Patients report drowsiness (sleep attacks) late in the afternoon or early in the evening, as well as early spontaneous awakening in the morning. When patients are allowed to maintain their own schedule, sleep is normal for the age, except for the advanced phase.

The exact mechanism of the development of the advanced phase is unknown, although genetic and environmental factors are known to be involved. Various members of the same family can be affected

by phase advance. Mutation of the *hPer2* gene has been found in individuals of the same family who are affected by this syndrome.

The prevalence in the general population is unknown, although it increases with age. It is estimated that it affects 1% of middle-aged adults and the elderly. The incidence is similar in both genders. One of the complications reported is the use of alcohol, sedatives, hypnotic agents or stimulants to treat insomnia and drowsiness symptoms, which can lead to abuse of these substances.

Treatment

The simplest treatment is to delay sleep time, at a rate of 1 to 3 h every 2 days, until the desired sleep period is achieved. This method is better accepted in the advanced phase than in the delayed phase, because intermediate hours do not surpass the desired waking period. The problem with the elderly is the lack of physical, mental or social activities that can keep them awake until the desired sleeping time. Phototherapy (exposure to intense light), applied late in the afternoon for 1 or 2 h, can readjust the biological clock within a few days. Seasonal variations of light/dark cycle duration, in locations far from the equator, can require exposure to artificial light in winter months.

Irregular pattern

Individuals affected by the irregular pattern type of sleep disorder present an undefined pattern of sleep-wake cycle circadian rhythm. Depending on the time of day, the patient can present chronic insomnia or excessive sleepiness. Naps are common at any time of day or night in this syndrome.

Included among the predisposing factors are inadequate sleep hygiene and lack of exposure to synchronizing external agents, such as sunlight, physical activities and social activities, particularly in the institutionalized elderly, and this can predispose to an irregular sleep-wake cycle pattern.

The physiopathology involves anatomical or functional abnormalities of the circadian timing mechanism, which can result in an anarchic pattern of waking and sleeping. This pattern can also be observed in association with neurological diseases, such as dementia, and in children with intellectual disabilities.

As would be expected, polysomnography, sleep diaries and actigraphy register the lack of a regular sleep-wake cycle pattern. Monitoring other circadian rhythms, such as body temperature, also demonstrates the lack of rhythmicity. Sleep diaries or actigraphy should be employed for at least seven days in order to demonstrate an irregular sleep-wake cycle pattern.

The sum of the total sleep time in 24 h is essentially normal for the age. To confirm the diagnosis, the differential diagnosis of this disorder should include other sleep disorders, clinical/neurological problems and the use/abuse of medications/illicit drugs.

Treatment

Strict compliance with desired time of the sleep period, together with filling waking hours with physical and social activities, can correct the disorder. Intense light, applied for 1 or 2 h at the desired waking time, can synchronize biological clocks. Melatonin at a dose of 3 mg late in the afternoon has proven useful in children with severe psychomotor deficit but not in elderly patients with Alzheimer's disease.

Non-24-h sleep-wake cycle

The non-24-h sleep-wake cycle disorder is also known as non-24-h sleep-wake syndrome or hypernyctohemeral syndrome. It is characterized by sleep symptoms that occur as a result of the longer (approximately 25-h) duration of the circadian timing mechanism cycle. Both insomnia and excessive sleepiness related to abnormal synchronization between the 24-h light/dark cycle and the endogenous sleep-wake circadian rhythm are likely to occur.

Blind individuals are more predisposed to this disorder.

Approximately 70% of individuals with total sight loss report sleep disorder, and 40% of those are diagnosed with cyclic, chronic sleep disorder. Rare cases have been described in individuals with normal vision, and the disorder can be induced by certain environmental conditions, such as isolation. Onset can occur at any age, and the disorder is congenital in blind children. If left untreated, it can become chronic.

The attempt to regulate the sleep-wake cycle can lead to abuse of alcohol, hypnotic agents, sedatives and stimulants, which can exacerbate the disorder. Depressive symptoms and mood disorders are typical comorbidities.

The lack of luminous input for the circadian pacemaker is clearly the cause of the non-24-h circadian rhythm. Sleep diaries or actigraphy for at least seven days demonstrate a sleep-wake pattern that typically delays every day, since it has a duration of approximately 25 h. The differential diagnosis should include other sleep disorders and clinical/neurological problems, as well as the use/abuse of medications/illicit drugs.

Treatment

Melatonin administered at appropriate times, at a dose of 0.5 mg, late in the afternoon, regulates the sleep phase.[26]

Secondary to a rapid change of time zone

Sleep disorder secondary to a rapid change of time zone is a temporary disorder, also known as jet lag syndrome, caused by the desynchronization between the sleep-wake cycle and the cycle generated by the circadian timing mechanism, usually after a trip during which at least two time zones are crossed. The syndrome is a temporary and self-limiting condition. Symptoms appear one to two days after the trip and disappear within one week. The most common complaints are sleep disorder, decreased alertness, altered cognitive function, malaise and gastrointestinal symptoms. The severity of the symptoms depends on the number of time zones crossed and the direction of the trip. Trips to the East, which require circadian rhythm advances, are usually harder to adapt to. Exposure to light at inappropriate hours can prolong the time to adjustment of the circadian rhythm.

The disorder affects all age brackets.

However, older people can present more pronounced symptoms. The cause is the desynchronization between environmental and endogenous day-night cycles, and the disorder is aggravated by the loss of sleep. Further investigation is not indicated, nor is polysomnography. We should recommend that, during the days following the trip, travelers avoid risk situations that require quick reflexes.

Treatment

Individuals taking flights to the East should wake up early and avoid bright light in the morning but should try to get maximum exposure to light late in the afternoon. Individuals taking flights to the West should force themselves to remain awake during the day and should take pains to avoid falling asleep before dark. There is evidence that melatonin at a dose of 2-5 mg, prior to sleeping on the first nights after arrival, is efficacious in preventing or reducing jet lag and should be recommended for those who cross more than four time zones.[27] Nonpharmacologic measures, such as avoiding the ingestion of alcoholic beverages, maintaining proper hydration and taking regularly scheduled naps, have been suggested.[28]

Secondary to working irregular hours

Sleep disorder secondary to working irregular hours is characterized by complaints of insomnia or excessive sleepiness, since the working hours coincide with the habitual sleep phase, causing shortened total sleep time and unsatisfactory quality of sleep. In this context, insomnia or excessive sleepiness are temporally associated with the work schedule that recurrently overlaps habitual sleeping time and typically manifest at least once a month. Shift work can be based on fixed hours or can be in swing-shifts. Sleep disorder is more frequent among individuals working night shifts or early morning shifts. The decreased alertness related to this disorder not only impairs work performance but can also increase the risk of accidents. Typically, the disorder will persist for as long as working hours remain irregular. However, in some individuals, the disorder remains even after working hours have returned to normal.

Since there is no definitively efficacious treatment for this disorder, patients are forced to live with the symptoms or forego the extra income from shift work. The efficacy of the use of stimulants to minimize the drowsiness of shift workers has been recently confirmed.[29]

The prevalence of this disorder related to irregular working hours depends on the prevalence of irregular working hours in the population. In industrialized countries, it is estimated that 20% of the work force consists of individuals who work irregular hours, and that 2-5% of these workers suffer from some sort of sleep disorder. Although little is

known regarding the consequences of this disorder, it is believed to be involved in the development of several diseases, such as hypertension,[30] breast cancer and uterine cervical cancer.[31]

Monitoring through the use of actigraphy or sleep diaries for a minimum of seven days, including episodes of night shift work, can contribute to confirming a temporal association. Polysomnography can be useful when the disorder is severe or when the etiology of the sleep disorder is in question.

Treatment

Intense light during working hours and the use of dark glasses in the morning at the time workers leave work can impede the secretion of melatonin at night and facilitate it during the day, synchronizing the sleep period with that of melatonin secretion. The use of hypnotic agents or melatonin prior to sleeping, for a limited time, can help fight insomnia. Drowsiness can be prevented with naps before the shift or during the shift break, as well as with the use of caffeine.

Secondary to diseases

A CRSD secondary to a disease primarily occurs as the result of a morbid clinical or traumatic process,[32] and its characteristics depend on the associated disease. The patient can present innumerable symptoms, including insomnia and excessive sleepiness, as well as altered sleep-wake cycle patterns such as the delayed phase, advanced phase or irregular pattern.

Insomnia or excessive sleepiness related to alterations of the circadian timing mechanism or to the lack of synchronization between the endogenous circadian rhythm and exogenous factors that affect the timing or the duration of sleep are likely to occur. The medical problem of the patient can explain the loss of synchronization that led to the CRSD. Inadequate sleep quality can cause neurocognitive symptoms and compromise physical performance, thereby aggravating or become confused with the subjacent profile.

Monitoring through the use of actigraphy or sleep diaries in order to register the circadian disorder for a minimum of seven days can confirm the association of the CRSD with the underlying disease. In the differential diagnosis, primary CRSDs, addressed above, should be ruled out, as should the use of illicit drugs or medications that alter sleep or the circadian rhythm.

Secondary to the use of drugs or medications

Cases of sleep disorders secondary to the use of drugs or medications meet the general criterion for CRSDs and are caused by either illicit drugs or medications.

Other types

The 'Other types' category of sleep disorders was created to accommodate the cases that meet the general criteria for CRSDs but do not meet the criteria for the other specific classifications.

Final considerations

In this article, we reviewed all diagnostic categories listed in the most recent edition of the ICSD, emphasizing the diagnostic aspects. With advances in the understanding of the causes of these disorders and the development of new tests,[33] diagnosis will evolve, allowing greater accuracy.

It is important that the diagnosis be correct, so that individuals with CRSD are not exposed to risks of accidents or unnecessary treatments (in some cases, for their entire lifetime)[34] such as the use of hypnotic agents without precise indication. Adequate sleep hygiene and phototherapy (exposure to intense light at scheduled times, according to the sleep disorder),[35] as well as the use of melatonin[36,37] or melatonin receptor agonists,[38] all constitute valid therapeutic options.

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