Review Article

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Circadian rhythm sleep disorders

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Circadian rhythm sleep disorders are common conditions manifested as misalignment between the sleep period and the physical/social 24-h environmental cycle. Delayed sleep phase (typical in adolescents) and advanced sleep phase (frequent in the elderly), situations in which the sleep period is displaced to a later or earlier time, respectively, are the two most prevalent circadian rhythm sleep disorders. There are, however, nine possible diagnoses of clinical interest. Since light is the main cue used in synchronizing the biological clock, blind individuals and night-shift/rotating-shift workers are more prone to develop circadian rhythm sleep disorders. In this article, the circadian rhythm syndromes included in the new International Classification of Sleep Disorders are reviewed as well as the most recent guidelines for diagnosis and treatment.

Key words Circadian rhythm - jet lag syndrome - melatonin - sleep disorders - sleep initiation and maintenance disorders - sleepiness

Introduction

Insomnia[1] and sleepiness are complex symptoms that are difficult to quantify due to the various dimensions that each one presents[2]. Among the causes of insomnia and sleepiness, possibly the most neglected ones are those related to circadian rhythm sleep disorders (CRSD)[3-5]. These disorders manifest as a misalignment between the sleep period and the physical/social 24-h environmental cycle, related to alterations in internal timing mechanisms. There are two typical patterns: one that is seen mostly in adolescents and one characteristic of elderly individuals. The adolescents' complaint can mimic insomnia when they go to bed at regular times and it takes them hours to fall asleep. However, it can also mimic sleepiness when they cannot get up in the morning. The elderly can appear to have sleepiness when they fall asleep at 2000 h, 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. These cases of pseudo-insomnia or sleepiness are actually the most common models of CRSD, with serious consequences in terms of quality of life. The CRSDs deserve careful management within evidence-based practice parameters[6].

Sleep and timing mechanisms

Timing mechanisms or oscillators have been discovered even in the most primitive living beings[7]. The ability to adapt to light/dark cycles and seasons improve the chances of survival on the surface of our planet[8]. Plants need to predict the presence or absence of sun to change its metabolism accordingly with the availability of energy or the need to save

energy. Animals, beyond of their 'spatial niche', need a 'temporal niche' to survive[9], a time when they are less exposed to predators and stand a greater chance of obtaining food[10]. In addition to day-night cycles, the adaptation to seasons is essential to survival in wild animals[11] and can be detected in humans[12]. The circadian clock is driven by transcription and translation feedback mechanisms that regulate the 24-h day-night rhythms with different DNA elements[13]. Seasonal behaviour is controlled by internal calendars[14] receiving environmental cues from day length and temperature, which are a function of the latitude.

Circadian oscillations of tightly regulated parameters like body temperature and hormone levels challenge the understanding of homeostasis as the stability of the 'milieu interieur'. This has been criticized for leaving aside the temporal implications of what is considered normal[15]. Is the nervous system in its normal state when it is awake or when it is asleep? Taking the temporal variations into consideration is paramount to understanding from biochemical to behavioural facets of living beings.

Homeostatic sleep propensity is the necessity of rest that builds up as a function of the length of time spent in activity since the last rest period. This may be related to adenosine accumulation during wakefulness[16]. Circadian rhythms determine the timing of a sleep episode based on the 24-h clock, independently from previous rest or activity. These two factors – homeostatic and circadian – interact to maintain the sleep-wakefulness cycle in "constant oscillation".

As a species, Homo sapiens is diurnal, adapted to be active during the light phase and rest during the dark phase of the 24-h cycle. The development of human visual system and our dependence on luminous information characterize us as a diurnal species[17]. The main sleep period in our species is, therefore, during the dark phase. However, there can be other moments of rest and activity over the course of the day.

The system that controls sleep-related behaviours is comparable to an orchestra[18,19], comprising various players[20]. The maestro that conducts the concert of the mammalian chronobiology is the suprachiasmatic nucleus (SCN)[21]. Located next to the optic nerve, this area of the hypothalamus receives connections from special fibers in the retina that inform the existence of light to the system. Melatonin[22] is secreted by the pineal gland, following the stimulus from the SCN in the absence of light, translating the photic information into chemical stimulus to all cells in the organism. Interestingly, there is evidence that exposing cultured neural retinal cells of chicken embryos to cycles of light and dark triggers rhythmic expression of clock genes[23].

The SCN interactions with non-visual light sensors alter the circadian rhythms. Intense light repositions the internal clock forward or backward depending on the phase of the cycle it is applied[24,25]. Luminous stimuli in the evening delay and early in the morning interrupt melatonin secretion.

The various aspects of human performance are inaccurately considered stable phenomena. Several lines of evidence derived from many laboratories, under natural or controlled conditions, and from manipulations of the sleep-wake cycle, demonstrate that performance is strongly affected by cyclic phenomena[26] which can be mathematically modelled[27]. Living organisms are not equipment that, once switched on, function uninterruptedly and with minimal oscillations[28]. Physical and mental oscillations in human performance are of relevant magnitude and impose risks[29] to adults and children[30]. Fatal accidents represent the gloomiest face of functioning deterioration associated with circadian rhythms.

The processes that control sleep cycles are subject to variations of such magnitude that may be of clinical interest. As any biological system, oscillators responsible for the regularity of the sleep-wake cycle suffer mutations[31] 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 other factors, such as ageing[32]; stress[33] chronotype (morningness or eveningness)[34]; and organic diseases[35].

Human beings maintain 24-h sleep-wake cycles. Typically, the sleep schedule is altered on weekends. Although its location has not been established, circaseptan (about seven days) and circasemiseptan (about half week) clocks may exist to adapt the organism to events that happen once and twice a week. These rhythms regulate different characteristics in specific fashions. For instance, the amplitude of mood oscillations for negative affective symptoms is larger in circasemiseptan and circaseptan domains than in circadian whereas positive affect shows ampler variation in the circadian domain[36]. Strengthening the case for the existence of a circaseptan clock is the fact

that in most plants and animals reproductive cycles are counted in weeks. Despite sufficient flexibility and numerous adaptation mechanisms to regularly occurring events, some alterations of the circadian cycle go beyond the limits of one's system ability to compensate for (Fig.). These alterations may represent CRSDs and may deserve specific treatment following correct diagnosis.

The most consistent classification of circadian disorders is in the second edition of the International Classification of Sleep Disorders (ICSD)[37], including new categories besides the six more common CRSDs, bringing the total number of possible diagnoses to nine (Table I). In this classification, to diagnose a CRSD demands certain conditions. In first place, a disorder must induce clearly defined symptoms of insomnia, excessive sleepiness or both, with social and/or occupational impairment. In second place, the disorder should be persistent or recurrent. In third place, the cause of the disorder must be related to the circadian clock, due either to alterations in timing mechanisms or to lack of synchronization between endogenous and exogenous circadian factors, affecting timing and/or duration of sleep. These considerations are important to keep in mind when diagnosing a CRSD. In face of an individual with impairing and chronic complaints, the physician should look for specific diagnoses such as those reviewed below.

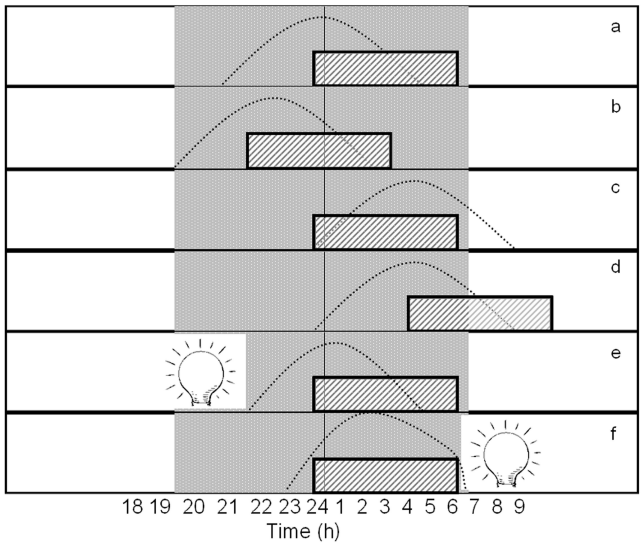

Fig. Diagrams representing melatonin secretion (dotted line) and the sleep period (dashed box) in normal individuals (panel a), individuals with advanced sleep phase disorder (ASPD; panel b) and individuals with delayed sleep phase disorder (DSPD; panels c and d). In normal individuals, melatonin secretion begins early in the evening and peaks around midnight, when the person lies down and falls asleep without difficulty; in the morning, the melatonin secretion has worn off, and the person arises without feeling sleepiness. In the advanced phase, melatonin peaks at 2200 h, causing irresistible sleepiness, and its effect wears off by 0400 h, resulting in early awakening. In the DSPD, if the individual tries to maintain a normal routine and goes to bed at 2300 h, 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 sleepiness will be maximal (panel c). If, however, the individual is allowed to go to bed and wake up at later hours, his/hers sleep quality will be normal (panel d). Phototherapy at the beginning of the night delays melatonin secretion in ASPD (panel e) and at the awakening interrupts melatonin secretion in DSPD (panel f).

Table I. Classification of circadian rhythm sleep disorders (CRSD)

CRSD
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
Source: Ref. 37

Circadian rhythm sleep disorders

(*1*) *Delayed sleep phase disorder*

Delayed sleep phase disorder (DSPD) is characterized by late sleeping and waking, on most nights, usually with a delay of more than two hours in relation to conventional or socially acceptable times. Patients report having difficulty to initiate sleep and desiring to wake up late. One important characteristic of this disorder is that if patients are able to follow an at-will sleep regimen, their circadian rhythm inevitably becomes persistently delayed, causing social life impairment. In this case, patients' sleep complaints are solved since their sleep is otherwise normal when the delayed sleep phase is accounted for. Several DSPD patients are self-treated by engaging nighttime occupations.

Family history can be present in up to 40 per cent of the individuals with delayed phase. The prevalence in the general population is 7 to 16 per cent. The age group more commonly affected is that of teenagers and individuals around 20 yr of age[38,39]. Estimated prevalence of DSPD is 10 per cent among all patients with chronic insomnia seeking medical assistance at sleep clinics[37].

The mechanism of the DSPD is unknown. Genetic factors, such as polymorphisms in the timing mechanism, principally of the human *Per3* gene, are associated with this syndrome[40]. Environmental factors, however, must be taken always in consideration. Exposure to light is important. Decreased light exposure in the morning and excessive light exposure late in the afternoon can exacerbate DSPD. Additionally, avoiding late hours for television and video-games may help improving the problem. Changes in work shifts and trips through several time zones can precipitate DSPD.

Treatment: In all CRSDs, it is fundamental to enforce the adequate use of sleep hygiene measures (Table II). Although these actions seem obvious, many patients totally ignore them, thereby making treatment impracticable. Deep-seated behaviours, such as ingesting high doses of caffeine at night, are considered non negotiable by most patients.

A useful way of treating DSPD is to further delay sleep initiation, at a rate of two or three hours every 2 days, until the desired time of sleep period is achieved, ideally from 2330 to 0700 h. This method may be acceptable because it is easier to prolong wakefulness than to anticipate sleep. In practice, however, the need for rigorous compliance with the regimen and inconvenient intermediate hours compromise treatment efficiency. Phototherapy (exposure to bright light), applied during 1 or 2 h at the desired waking up time readjusts the biological clock after a few days but also has practical limitations. A timer may be set to turn bright lights on at the desired wake up time; a dawn simulator may be more tolerable. Portable lightening equipment may be necessary to follow the individual in different rooms and outdoors. Melatonin late in the afternoon advances the sleep phase. The dose is titrated from 0.3 to 3 mg[4].

Table II. Sleep hygiene measures for patients with circadian rhythm sleep disorders

Show consideration for 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
Relax and sleep:
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
Beware of drugs and disruptive environments:
Prior to sleeping, avoid products that contain alcohol, tobacco, caffeine or any substance that acts on the central nervous system
Ensure that the bed is comfortable, with mattress, sheets, and covers appropriate for the temperature
Ensure that the bedroom is dark and quiet, with a temperature around 24°C (ranging from 17 to 27 °C)

(*2*) *Advanced sleep phase disorder*

Advanced sleep phase disorder (ASPD) is characterized by early sleeping and waking times, on most nights, usually several hours before conventional or socially acceptable times. Patients report sleepiness and sleep bouts late in the afternoon or early in the evening, as well as early spontaneous awakening in the morning, simulating insomnia. When an at-will sleep schedule is permitted, sleep hours are advanced while patients' sleep becomes normal for the age, confirming phase advance as the reason for the symptoms. The mechanism of the ASPD is unclear, although genetic and environmental factors are known to be involved. Familial advanced sleep phase phenotype was the first CRSD to have its mendelian inheritance characterized. Polymorphism of the human *Per2* gene and a mutation in the casein kinase I gene have been found in individuals of the same family who are affected by this syndrome[41,42]. The Per2 gene has also been associated with depression[43].

The prevalence in the general population increases with age. It is estimated that it affects 1 per cent of middle aged adults and the elderly. The incidence is similar in both genders[37]. One of the reported complications of ASPD is the use of alcohol, sedatives, hypnotic agents or stimulants to treat insomnia and sleepiness symptoms, which can lead to abuse of these substances.

Treatment: A recent review on the management of sleep disorders in older persons includes the treatment of ASPD[44]. The simplest measure is to delay sleep time, at a rate of one to three hours every 2 days, until the desired sleep period is achieved. This method is better accepted in the advanced sleep phase than in the delayed sleep phase, because intermediate hours do not encompass the desired waking period. The difficulty with the elderly population is the lack of physical, mental or social activities that can keep them awake until the desired sleeping time. Phototherapy, applied late in the afternoon for one or two hours, can readjust the biological clock within a few days. Seasonal variations of light/dark cycle duration, in locations at

high latitudes, can require exposure to artificial light in winter months[4].

(3) Irregular sleep-wake rhythm

Individuals affected by the irregular sleep-wake type of CRSD present an undefined pattern of sleep-wake rhythm. The patient can complain either of chronic insomnia or of sleepiness, depending on the particular necessity at that moment; if he/she needs to be awake in a time sleep propensity is high the symptom will be sleepiness. In this syndrome, instead of one consolidated sleep period, sleep consists mostly of naps at any time of day or night. This pattern can be observed in association with neurological diseases, such as dementia, and in children with intellectual disabilities. The association with dementia and the anarchic sleep-wake pattern seen in animals after the SCN is destroyed[45], indicate that anatomical or functional abnormalities of the SCN clock are possible causes of irregular sleep-wake rhythm. Included among the predisposing factors are inadequate sleep hygiene and, particularly in the institutionalized elderly, lack of exposure to synchronizing external agents, such as sunlight, physical and social activities.

Sleep diaries and actigraphy are useful to confirm objectively the lack of a regular sleep-wake schedule and should be employed for at least seven days in order to demonstrate the erratic sleep-wake pattern. Complex diagnostic tools, such as polysomnography, and circadian monitoring of body temperature also demonstrate the lack of rhythmicity, but are unnecessary for clinical purposes. The sum of the total sleep obtained in 24 h is essentially normal for the age. The differential diagnosis of this disorder should include other sleep disorders, clinical or 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 one or two hours at the desired waking time, can synchronize internal clocks. A late in the afternoon dose of 3 mg of melatonin can be useful to control symptoms of children with psychomotor deficit but not of dementia patients[4].

(4) Non 24-h sleep-wake syndrome

Also known as nonentrained type CRSD, hypernychthemeral syndrome or free-running type CRSD, this disorder is characterized by sleep symptoms that occur as a result of the longer (approximately 25 h) duration of the circadian timing mechanism cycle. The symptoms occur in a variable fashion depending on the specific phase the endogenous sleep-wake circadian clock is in relation to the 24-h light/dark cycle. Both insomnia and excessive sleepiness alternate during the 23 days of desynchronized phase until the 25-h internal clock resynchronizes to 24-h external timekeepers.

This disorder occurs in individuals unable to receive the light-dark external clues. Approximately 70 per cent of individuals with total sight loss report sleep disorder, and 40 per cent of those are diagnosed with cyclic, chronic sleep disorder[46]. Rare cases have been described in individuals, mostly teenager males, with normal vision[47]. Also, the disorder can be induced by certain environmental conditions, such as isolation. Onset in blind people is simultaneous with the loss of sight, being congenital in blind children. If left untreated, it can become chronic.

Abuse of alcohol, hypnotic, sedative, and stimulant agents can exacerbate the disorder. Frequently the substances are used in the attempt to regulate the sleep-wake cycle. Depressive symptoms and mood disorders are typical co-morbidities.

The cause of the non 24-h circadian rhythm is easily attributed to the lack of light signal for the circadian clock system. Sleep diaries or actigraphy are valuable instruments in the diagnosis. Used for long periods, ideally a month, but at least for seven days, the tracing obtained unmistakably demonstrate a sleep-wake pattern that delays one hour every day, since the internal cycle has a duration of approximately 25 h. The differential diagnosis includes sleep disorders and problems of clinical and neurological origin. In every sleep disorder abuse of alcohol, medications, and illicit drugs must be excluded before closing a diagnosis.

Treatment: Melatonin replacement therapy, administered at low physiological doses, around 0.5 mg, late in the afternoon, is the only evidence-based treatment to regulate the sleep phase[48].

(5) Jet lag disorder

Time zone change syndrome or jet lag is caused by the temporary divergence between the environmentally adequate sleep-wake cycle and the endogenous cycle generated by the circadian timing mechanism, usually after a trip during which at least two time zones are crossed. The syndrome is a self-limited condition and may be aggravated by the loss of sleep. The disorder lasts a few days; starts one to two days after the

arrival and resolves spontaneously within one week. The usual complaints are insomnia or sleepiness, impaired alertness, cognitive problems, malaise and gastrointestinal illness. Depending on the direction of the trip and how many time zones are crossed the symptoms may vary from minimal to severe. Trips requiring circadian clock advances, to the East, are more prone to cause sleep disorder. Exposure to light can help to resolve or to prolong the disorder. The disorder affects all age brackets. Older people, however, can present more pronounced symptoms. Further investigation is not indicated, nor is polysomnography.

Treatment: Treatment is indicated to avoid occupational risks for airline crew and to prevent ruining the enjoyment of travelers. Exposure to light or light avoidance can help to synchronize local to internal clocks. The phase-response curve to light has a six-hour window when light should be avoided and a six-hour window when light exposure should be maximized. In the first days, travelers to the East should avoid light at destination in the hours corresponding from 2100 to 0300 h at their origin, *i.e*., at the time of melatonin peak in their internal clocks. These travelers should receive bright light when the hour at origin is between 0500 and 1100 h. People in flights to the West should avoid light from 0500 to 1100 origin time and encourage light exposure between 2100 and 0300 h origin time. As the internal clock adjusts to local time, the light exposure time changes by 1-2 h[49].

Pharmacological interventions may be necessary. Caffeine is useful to reduce fatigue[50]. Meta-analysis data confirm that melatonin at a doses varying from 2 to 5 mg, at bedtime, on the first nights after arrival, prevents or reduces jet lag symptoms[51]. The recommendation, also based on meta-analysis, is that travelers crossing more than four time zones take melatonin[52]. Maintaining hydration, eating fruits, taking naps, and avoiding ingestion of alcohol are useful suggestions[53]. It is recommended that, during the days following the trip, travelers avoid risky situations that require fast reflexes[3].

(6) Shift work disorder

Sleep disorder secondary to working irregular hours is characterized by complaints of insomnia or excessive sleepiness, when the working hours coincide with the habitual sleep phase, causing shortened total sleep time and inadequate sleep quality. In this context, insomnia or excessive sleepiness are temporally associated with the work schedule that recurrently overlaps habitual sleep time and typically manifest at least once a month. Sleep complaints are more prevalent among workers of night shifts or of early morning shifts. This disorder, besides impairing work performance, also increases the risk of accidents due to decreased alertness[54]. The disorder tends to persist while working hours irregularity persists. However, in some individuals, the complaint remains even after working hours have returned to normal. Since there is no definitively efficacious treatment for this disorder, workers are forced to live with the symptoms or forego the extra income derived from shift work.

The prevalence of this disorder depends on the prevalence of irregular working hours in the population. In industrialized countries, it is estimated that up to 20 per cent of the work force works variable hours and that 2 to 5 per cent of these workers suffer from some sort of sleep disorder[37]. Although little is known regarding the consequences of this disorder, it is believed to be involved in the development of diseases such as hypertension[55], breast cancer and uterine cervical cancer[56].

Monitoring with actigraphy or sleep diaries for at least seven days, including nights of shift work, can contribute to confirm a temporal association between symptoms and shift work. Polysomnography is indicated in cases of severe or questionable sleep disorder.

Treatment: The efficacy of the use of stimulants to minimize the sleepiness of shift workers has been recently confirmed[57]. Exposure to intense light during work and avoidance of light by the use of dark glasses at the time workers leave work can prevent melatonin secretion at night and stimulate it during the day, helping to synchronize sleep to melatonin secretion. To fight insomnia, short-term use of a hypnotic agent or melatonin prior to sleeping can be helpful[3]. Sleepiness can be prevented with naps before the shift or during the shift break, as well as with the use of caffeine[58].

(7) CRSD due to medical conditions

This occurs as the result of a morbid clinical or traumatic process[59], and its characteristics depend on the associated disease. The patients can present numerous symptoms related to their medical condition, besides insomnia and excessive sleepiness, as well as a CRSD such as the delayed phase, advanced phase or irregular sleep-wake rhythm.

Insomnia or sleepiness occur due to desynchronization between the affected endogenous circadian clock and the exogenous timekeepers, affecting timing or duration of sleep. The patient's medical condition can explain the loss of synchronization that led to the CRSD. Poor sleep quality leads to neurocognitive symptoms and impairs physical function, thereby aggravating the subjacent disease and becoming indistinguishable from it.

Actigraphy or sleep diaries for a minimum of seven days can confirm the association of the CRSD with the underlying disease. In the differential diagnosis, primary CRSDs should be ruled out, as should the use of illicit drugs or medications that alter sleep or the circadian rhythm. Melatonin has been considered helpful to improve sleep of patients with asthma[60], chronic obstructive pulmonary disease[61], Parkinson's disease[62], and on hemodialysis[63].

(8) CRSD due to drug or substance

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

(9) Other CRSD

This category of sleep disorder 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

All diagnostic categories listed in the recent edition of the International Classification of Sleep Disorders[37] were reviewed, emphasizing the diagnostic aspects, so to allow the clinician to recognize and treat individuals with CRSD. Advances in the understanding of the causes of these disorders and the development of new genetic tests[64], will improve diagnosis, allowing greater accuracy.

A correct diagnosis is paramount in achieving the best outcome, so that individuals with CRSD are not exposed to accidents and unnecessary treatments. In some cases, wrong diagnoses result in the use of hypnotic agents without correct indication for an entire lifetime[65,66]. Adequate sleep hygiene and phototherapy (exposure to intense light at scheduled times, according to the sleep disorder)[67], as well as the use of melatonin[68,69] or melatonin receptor agonists[70], are suitable therapeutic options in several CRSDs.

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