At the crossroads of epilepsy and sleep: some issues

Na encruzilhada da epilepsia e do sono: algumas questões

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ABSTRACT

There is a close association between sleep and epilepsy, and this literature review aims to raise issues regarding sleep time control, circadian and ultradian rhythms, epilepsy and its interaction with sleep and circadian rhythm, epilepsy and sleep disorders, and finally epilepsy management and medications. It is mentioned that sleep may provide a hypersynchronous state, as occurs in non-rapid eye movement sleep (NREM), and hyperexcitability, in cyclic alternating pattern (CAP), allowing more frequent interictal epileptiform abnormalities and seizures. In some epilepsy syndromes, seizures occur broadly / or entirely during sleep or on awakening, mainly in childhood, and maybe exacerbated in adults during the sleep or sleep-deprived, and there are the so-called Sleep-related epilepsies that are divided as sleep-associated, sleep-accentuated and arousal/awakening related. Sleep quality may be reduced in patients with epilepsy also due to nocturnal seizures or concomitant sleep disorders. Sleep disorders are common in patients with epilepsy and treatment of them mainly sleep-disordered breathing may improve seizure control. Besides, some parasomnias may mimic seizures, and also they can adversely affect the quality and quantity of sleep whereas antiepileptic therapy can have a negative or positive effect on sleep. Nocturnal epileptic seizures may be challenging to discern from parasomnias, in particular NREM parasomnias such as night terrors, sleepwalking and confusional arousals.

Keywords: Epilepsy, sleep, sleep disorders, neuronal excitability; seizures; circadian rhythms.

RESUMO

Há uma estreita associação entre sono e epilepsia, e esta revisão de literatura tem como objetivo levantar questões relacionadas ao controle do tempo do sono, ritmos circadianos e ultradianos, epilepsia e sua interação com sono e ritmo circadiano, epilepsia e transtornos do sono e, finalmente, o tratamento e medicamentos para epilepsia. Menciona-se que o sono pode proporcionar um estado hipersincrônico, como ocorre no sono "non-rapid eye movement" (NREM), e hiperexcitabilidade, no "cyclic alternating pattern" (CAP), permitindo anormalidades epileptiformes interictais e crises epilépticas mais frequentes. Em algumas síndromes epilépticas, as crises ocorrem ampla / ou inteiramente durante o sono ou despertar, principalmente na infância, e podem ser exacerbadas em adultos durante o sono ou privação de sono, e as chamadas epilepsias relacionadas ao sono se dividem em sono associadas, sono acentuadas e relacionadas com o despertar. A qualidade do sono pode ser reduzida em pacientes com epilepsia também devido a crises epilépticas noturnas ou transtornos do sono concomitantes. Esses são comuns em pacientes com epilepsia e o seu tratamento, principalmente dos transtornos respiratórios do sono, pode melhorar o controle das crises epilépticas. Além disso, algumas parassonias podem mimetizar crises epilépticas, e também elas podem afetar adversamente a qualidade e a quantidade do sono, enquanto a terapia antiepiléptica pode ter um efeito negativo ou positivo sobre o sono. Pode ser difícil discernir as crises epilépticas noturnas das parassonias, em particular das parassonias NREM, como terrores noturnos, crises de sonambulismo e despertares confusionais.

Palavras-chave: Epilepsia, sono, distúrbios do sono, excitabilidade neuronal; convulsões; ritmos circadianos.

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INTRODUCTION

Over time, there has been a growing understanding of the important and complex relationship between sleep and epilepsy, to be emphasized in this article, but seizures can occur at any time of the day or night, however, some have some kind of relationship with the sleep, which are classified as sleep-related epilepsies.

There is still the question of the periodicity of expression of seizures in several patients with epilepsy (PWEs), with ultradian to circannual expression, configuring 'seizure cycles', in addition to the presumed permissive role of sleep in promoting seizures in nocturnal epilepsy[13 14].

The mutual relationship between sleep and epilepsy has been known since Hippocrates and Aristotle. Many other leading physicians improved this understanding, primarily at the John Hughlings Jackson School, but soon the German and American Schools made their contribution: Hans Berger with the recordings of the first human brain EEGs; Frederic Gibbs and Erna Gibbs with the demonstration of significantly enhancement of interictal epileptiform discharges (IEDs) by sleep; Dieter Janz with the Study of Juvenile Myoclonic Epilepsy[6]. In recent years, the development of long term intracerebral electrode implants presented more accurate information about brain electrophysiology regarding epilepsy and also wakefulness and sleep[5 14].

More precisely, the frequency of sleep-related epilepsy, defined as "seizures that occur exclusively or predominantly during sleep", represents 10 to 15% of all epilepsies [5 8].

As for seizures, they correspond to an exaggerated and/or hypersynchronous activity of cortical neurons that produce transient neurological symptoms, with epilepsy being a chronic neurological disorder. This is represented by a seizure propensity for two or more distinct unprovoked or reflex seizures for more than 24 hours or an unprovoked or reflex seizure in an individual at high risk of subsequent seizures, in addition to the case of a diagnosis of epilepsy syndrome, as defined by International League against Epilepsy (ILAE).

The latest ILAE 2017 classification divides epileptic seizures into focal seizures (motor and non-motor, with or without altered consciousness, uni-hemispheric or bilateral), generalized seizures (motor - tonic-clonic or myoclonic - or non-motor - absences) and seizures of unknown origin, motor and non-motor. The etiology of epilepsy is classified as structural, genetic, infectious, metabolic, autoimmune, or of unknown origin[3].

Approximately more than 50 million people worldwide suffer from epilepsy, with the median prevalence of active epilepsy being 4.9 per 1,000 (2.3–10.3) for developed countries and 12.7 per 1,000 (3.5 –45.5) and 5.9 (3.4–10.2), in rural areas and urban studies, in developing countries according to Ngugi et al.[17].

A bidirectional relationship between epilepsy and sleep has been established, suggesting the existence of common neurobiological mechanisms, and the study of this complex relationship may improve understanding/control of the impact of epilepsy on sleep and vice versa[4 8] However, there is much more, as clusters of seizures and IEDs have also been shown to exist in a cyclic multidien pattern (several days) or beyond, as will also be discussed in this text.

CIRCADIAN / ULTRADIAN RHYTHM

Seizure patterns detected in PWEs suggest that circadian rhythms and sleep/wake mechanisms play some part in the disease, so it is important to know their basic mechanisms [19].

There are several conceptual models to justify the regulation of the sleep-wake rhythm, such as the two processes (Process C and Process S), in addition to the fact that the states of wakefulness and sleep are maintained by different populations of neurons. The main regulation mechanisms of sleep time control are shown in Figure 1.

The sleep-wake rhythm is mainly controlled by sleep homeostasis or sleep pressure (Process S) and the internal/body clock or circadian clock (Process C). The first is driven by the sleep debt that is influenced by the duration of wakefulness, and the second is an internal timing system with a period of almost 24 hours where almost every tissue in the body has its peripheral clock, which helps to maintain the physiology of the circadian tissue site, but the central clock is located in the suprachiasmatic nucleus (SCN), which synchronizes all peripheral clocks. This transmits stimulatory signals to arousal networks that promote wakefulness against the homeostatic urge to sleep. The accumulation of adenosine, but also of other substances that facilitate sleep, can decrease the activity of areas that influence wakefulness, as well as disinhibit the areas that promote sleep.

Regarding Process C, it can be regulated by various levels of endogenous products (which oscillate in a circadian rhythm) as well as by external stimuli (zeitgebers). Circadian rhythms (eg, cycles of physical, mental, and behavioral changes that the body undergoes in a 24-hour cycle) are primarily affected by the photic stimulus and are controlled by the suprachiasmatic nucleus (SCN).

Thus, when there is a decrease in daylight, there is a reduction in the inhibitory signalling of CNS projections to the pineal gland, which allows the secretion of melatonin.

The circadian rhythm also gives rise to nocturnal and diurnal variations in human vital activities, and it can affect both physiologically and pathologically the brain, as well as in the regulation of the sleep-wake cycle.

In addition, ultradian rhythms, with less than 24 hours, are important for various daily activities such as sleep cycles. This occurs in human sleep made up of 4-5 cycles (approximately every 90 minutes during the night) that include phases (REM - rapid eye movement and NREM - non-rapid movement)[2].

Regarding the areas of the brain committed to sleep-wake regulation, many are located in the hypothalamus and pons: two ascending pathways stimulate the maintenance of wakefulness (acetylcholine-producing neurons mainly active during wakefulness and REM sleep; monoaminergic neurons, more active during wakefulness); on the opposite side, neurons that act mainly during sleep and release the inhibitory neurotransmitters galanin and GABA. Thus, the sleep-wake regulatory circuit resembles a self-reinforcing loop, called the 'flip-flop switch' by Saper *et al*. 2005, apud Deboer[2]. This model of mutually excitatory and inhibitory circuits justifies the probability of a sleep-wake transition. Furthermore, neurons in the lateral hypothalamus releasing orexin/hypocretin appear to be a stabilizing component of the network and would increase arousal without inhibiting the ventrolateral preoptic area (VLPO) that stimulates sleep[2]. Concerning the central circadian pacemaker, the suprachiasmatic nucleus must be able to influence the activity of these active centers of sleep and wakefulness in the brain.

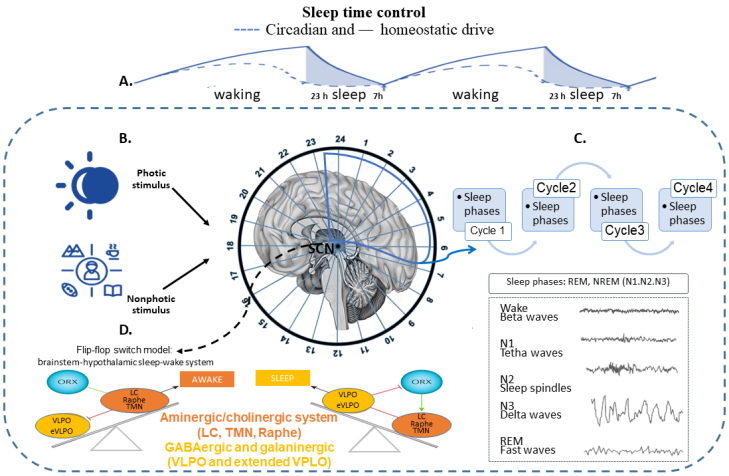

Figure 1. Sleep time control. Sleep homeostasis and the circadian clock.Circadian and ultradian rhythms, besides homeostatic factors, are the key core of it.
A. Sleep-wake is mainly controlled by two processes: sleep homeostasis or sleep pressure (Process S) and the internal/body clock or circadian clock (Process C). B. Circadian rhythms (e.g., the cycle of physical, mental, and behavior changes that the body goes through in a 24-hour cycle) are mostly affected by photic stimulus and are controlled by the SCN. C. Ultradian rhythms last fewer than 24 hours as occurs in human sleep composed of cycles. D-Brain areas committed to sleep-wake regulation[2 21]

FiLC = locus coeruleus, adrenergic, raphe nuclei, serotoninergic, TMN = tuber mamillare, histaminergic, LDT/PPT: = lateral dorsal tegmental/pedunculopontine, cholinergic; VLPO=ventrolateral preoptic área; SCN must be able to influence the activity of these active centers of sleep and wakefulness in the brain; SCN=suprachiasmatic nucleus.

EPILEPSY AND ITS INTERACTION WITH SLEEP AND CIRCADIAN RHYTHM

Sleep has an important influence on the expression and frequency of both seizures and IEDs, and the mechanism by which NREM sleep facilitates them likely relates to physiological hypersynchrony and thalamocortical oscillatory neural activity during NREM sleep, as reflected on electroencephalography by sleep spindles. Besides, sleep is now thought to promote IEDs by inducing state-dependent neuronal synchrony[13 14]. As NREM sleep progresses, responsiveness to external stimuli progressively decreases and the arousal threshold increases, in parallel with increasing delta frequency power. Slow-wave sleep is the state of maximum synchronicity in the brain while K complexes and sleep transients that are often correlated to epileptiform activity during lighter stages of sleep are related to patterns of periodic arousal instability as it is described by the cyclic alternating pattern (CAP), both indicating the relation to the hyper synchronization and hyperexcitability which characterize epileptiform activity.

Figure 2 outlines the sleep-related mechanisms of epilepsy, and the effects of shared networks and cerebral cortical instability to be unfolded below.

There is additional evidence indicating that the important role of NREM sleep is memory consolidation[8]. During NREM 3 sleep, repeated neuronal replay of episodic memory traces in the hippocampus leads to a gradual transformation and integration of these in neocortical networks[8]. Besides, sleep spindles, slow oscillations, and hippocampal ripples during NREM sleep provide and represent the neurobiological scaffold for reactivating memory traces learned awake, processing them, and channelling them for integration in neocortical sites for long-term storage[8]. Halasz *et al*.[9] discussed thoroughly the strong bond between NREM sleep and epilepsy and their effect on brain plasticity, as sleep relatedness may manifest in the enhancement of interictal epileptic discharges as spikes and pathological ripples. These events anddifferent sleep constituents as sleep slow waves, spindling and high-frequency oscillations are known to play an essential role in memory and learning. The mentioned authors defined three major groups of epilepsies: absence epilepsy mainly involving the thalamocortical system, where sleep spindles transform to generalized spike-wave activity; mesio-temporal epilepsy affecting the hippocampal declarative memory system where the sharp-wave ripples derail to dysfunctional epileptic oscillations; idiopathic childhood epilepsies that affects the perisylvian network may progress to catastrophic status electricus during NREM sleep.

IEDs and seizures are activated by NREM sleep and are least likely to occur during REM sleep in both focal onset and generalized epilepsies. NREM sleep activates generalized IEDs more than focal IEDs[8]. As it was presented IEDs can either be activated or inhibited depending on the sleep phase: likely to propagate during NREM as this is a more synchronized state as sleep spindles and high amplitude delta waves, but during REM sleep, there are asynchronous cellular discharge patterns that make epileptic EEG potentials less likely to propagate.

Several studies independently attest that in REM sleep there is a markedly low proportion of seizures, this phase of sleep being the most protective against focal seizures, generalized seizures, focal interictal discharges and specific epileptic syndromes[16]. Besides, REM sleep has an additional protective effect compared to wakefulness,

mainly regarding focal seizures, but it is not important for focal IEDs[16]. Also, IEDs during REM sleep tends to be more restricted and localizing, a potentially useful diagnostic localizing feature in patients undergoing preoperative evaluation for epilepsy surgery. Besides, clinically overt seizures occur most frequently during lighter stages of NREM sleep (N1and N2)[5]. Finally, sleep deprivation has been correlated to seizure inducing and precipitating IEDs possibly by inducing NREM sleep but also by affecting cortical excitability. However, sleep deprivation induces seizures in only some PWEs, mainly in that with genetic generalized epilepsies, especially juvenile myoclonic epilepsy[8].

Likewise, high-frequency pathological oscillations, a promising biomarker for identifying the epileptogenic zone, is more frequent in NREM sleep but less frequent in wakefulness and REM sleep[8].

Besides, the propensity for seizures that originated in the frontal lobe occurs predominantly during sleep, while temporal and occipital seizures are prevalent during wakefulness[12]. In addition, the sleep instability increases and/or modulates the occurrence of minor motor events and other sleep disturbances, which in turn facilitates the production of IEDs and sleep-related seizures by sustaining sleep instability and marked sleep instability is often observed in PWEs[5].

Through ascending cholinergic brainstem connections, REM sleep is physiologically characterized by rapid low-voltage activity on the EEG, REMs, and muscle atony[16]. It, as already mentioned, has also been shown to be useful in locating epileptogenic foci with potential translation into surgical efficacy.

The continuous corticothalamic firing of NREM sleep that normally produces spindles can transform into absence seizures, in the slow-wave phase. Based on sleep connectivity data, Ng and Pavlova[16] hypothesize that the influence of REM sleep on seizures is due to a desynchronized EEG pattern that reflects unique connectivity to this stage of sleep.

The CAP has been increasingly used in recent years as a marker of sleep instability. Overall, interictal epileptic expressions appear to be linked to slow sleep oscillations and particularly to delta reactive bursts characterized by the A1 subtype of the CAP system[11].

The occurrence of IEDs during NREM sleep is associated with the CAP, which is characterized by the regular alternation of the two EEG patterns: arousal complex phase A and post-arousal rebound response phase B. Phase A is composed of EEG rhythms of sleep oscillating with periodic stage-related arousal complexes such as K complexes, bursts of delta waves, and arousals, this phase is followed by the inhibitory phase B. Moreover, IEDs occur more often in phase A. EEG synchronization is the underlying factor for set off IEDs activity during NREM sleep. Regarding REM sleep, in the phasic REM sleep, there is increased EEG desynchronization mediated by high cholinergic neurotransmission that has a more suppression effect on IEDs than tonic REM sleep. This last expresses decreased EEG desynchronization mediated by low cholinergic neurotransmission[12]. Consequently, it is well known that most sleep-related seizures occur in NREM sleep during periods of unstable sleep such as stage changes and the CAP[5].

Halász[10], in 2015, already conceptualized that both absence and nocturnal frontal lobe epilepsies are epilepsies of the sleep-wake system that represent epileptic disorders of the antagonistic sleep/awakening network. This conception is based on the thalamocortical system and its brainstem connections that contain two antagonistic loopsdealing with the sleep and awakening network.

The sleep network is responsible for triggering a suppression burst and intrathalamic circuit connecting reticular inhibitory nuclei with thalamus-cortical relay neurons that produce spindles and slow waves. Consequently, absence epilepsy must be explained as that linked to the corticothalamic triggering mode of NREM sleep, released by the evoked oscillations of the level of alertness defined by the reactive response of slow waves.

On the other hand, the wake network coincides with the ascending reticular system and the thalamic connections that allow influences from cholinergic excitation and inhibit the reticular nuclei, thus providing a tonic flow of thalamus-cortical neuronal discharge. Thus, in the genetic variation of nocturnal frontal lobe epilepsy, the ascending cholinergic excitation system plays a crucial role, making hyperexcitable the excitation system.

The antiepileptic drug also affects sleep quality and architecture, indeed it is still acknowledged that it improve seizure control and sleep fragmentation, may also have different effects on sleep architecture in PWEs[4].

The Sleep-related epilepsies can be divided between sleep-associated (The majority are focal onset and include: benign focal epilepsies of childhood, such as benign epilepsy with centrotemporal spikes, Panayiotopoulous syndrome, and sleep-related hyper motor epilepsy), sleep-accentuated (electrical status epilepticus of sleep, Landau-Kleffner syndrome, West syndrome, and Lennox-Gastaut syndrome) and arousal/awakening related (juvenile myoclonic epilepsy and epilepsy with generalized tonic-clonic seizure)[8,18].

Included in these is sleep-related hyper motor epilepsy, previously named frontal lobe nocturnal epilepsy, as 30% of cases are extra-frontal and seizures are sleep-related, not time-related, and the predominant semiology is hyper motor[8].

Inasmuch, the close relationship between circadian rhythm and epileptic seizures has been increasingly studied, including their possible circadian pattern. With the development of the stereo-EEG, it was possible to present relevant information about network activation in sleep-related epilepsies, the cyclic pattern distribution, and the

definition of the epileptogenic zone. A growing research area is in circadian biology and epilepsy, as about 90% of people with epilepsy have seizures with a circadian pattern, in part related to sleep itself[8 14].

Important questions are how seizures and epilepsy disrupt the expression of central clock genes and how disruption of clock mechanisms impacts seizures and the development of epilepsy[19]. Consequently, the effect of sleep on seizure is also closely related to the circadian rhythms that include cortisol, known to be related to epileptiform activity[23].

In addition, recent studies provide insight into the potential circadian drivers of epilepsy by elucidating the gene expression pathways underlying the oscillating function of CNS neurons and also by studying parallel pathways in epileptogenic regions of the brain that may provide a basis for understanding the links between circadian rhythms and seizures or epilepsy at the molecular level[19].

Besides, chronic recordings of brain activity in humans and animals have yielded converging evidence for the existence of cycles of epileptic brain activity that operate over diverse timescales: daily (circadian), multi-day (multidien) and yearly (circannual) not fully explained by the differential effects of sleep phases on seizures[13 14]. Regarding these phases, it is remembered that there are main human cycles such as the 24 h sleep/wake cycle (circadian) and multiple sleep cycles (ultradian), of about 4-6 cycles of 90 min each, comprising sleep phases: REM (random eye movements) or NREM (non-REM). The first is less likely to express seizures.

Karoly *et al*.[14] present the hypothesis that as there are multiday cycles in other spheres of human physiology and disease this rhythmicity in epilepsy do not arise only because of epileptogenesis or ictogenesis, but, systemic physiological rhythms may combine into complex, individual-specific oscillations pro-ictal conditions. Also, Baud *et al*.[1] refer that the concept of a direct, generalizable relationship between IEA and seizures is challenged, as there is a better hypothesis that these epilepsy phenomena covary under the differential influence of factors operating at multiple timescales.

The seizures may occur in a predictable pattern over a month, week, day or randomly, and they may be associated with sleep-wake states[19]. Figure 3 presents seizure and IEDs timing to fluctuating influenced by different modulators, including the sleep-wake rhythm.

There is a focus on the imbrication between mechanisms of circadian-associated modifications in SCN neuronal excitability and mechanisms of epileptogenesis as an important identification mechanism pathways and molecules that could show targets or strategies for epilepsy therapy[19]. Besides, membrane excitability also has circadian rhythmicity, as, e. g., in the suprachiasmatic nucleus, potassium currents culminate in the evening to dampen clock neurons, and several neurotransmitters that adjust neuronal or membrane excitability also have circadian fluctuation in their expression. However, in an epileptic brain, this typical physiology may be changed, leading to modification in excitability during distinct vigilance states or in a circadian aspect[13 14 15].

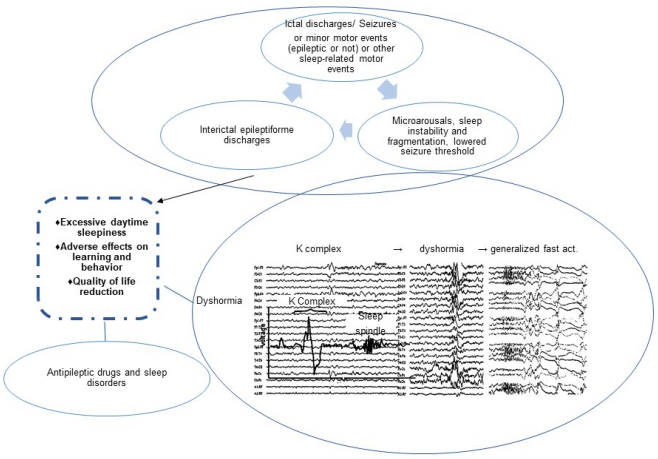

Figure 2. Sleep-epilepsy effects. The sleep mechanism and the commonly shared networks between sleep and epilepsy and the resulting outcomes, a vicious cycle, as nocturnal seizures can interrupt sleep while some factors, including antiepileptic drugs and sleep disorders, all may contribute to sleep fragmentation that can worsen seizures[4]. Most sleep-related seizures are followed by awakening or arousal, with IEDs being related to pre-or post-arousals, which likely contributes to sleep/wake complaints[8]. Many internal triggers facilitate the occurrence of micro-arousals and sleep instability that increases and/or modulates the occurrence of minor motor events and other sleep disturbances, which in turn induces IEDs and sleep-related seizures[5]. A link between sleep and seizures is seen in clinical neurophysiology employing the "dyshormia", the overlap of epileptiform discharges and K-complexes – microarousals, a term coined by Niedermeyer that implies in paroxysmal responses to arousing stimuli, either electrographically or with clinical seizures, typically seen in genetic generalized epilepsy, but also focal epilepsy temporal spikes may occur in conjunction with K complexes. "Arousal signals trigger thalamic activation and focal or bilateral synchronous spikes in a regionally or multiregional electrically hyperexcitable cortex" (Koutroumanidis *et al*., *apud* Unterberger *et al*.)[22 24].

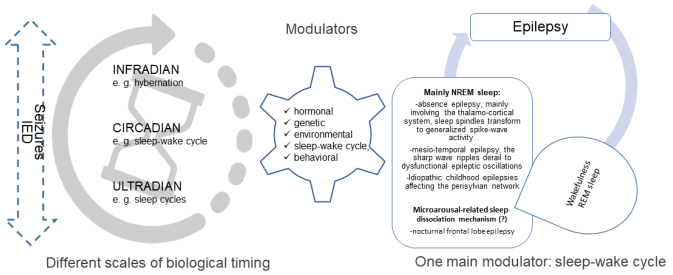

Figure 3. Seizure and IEDs timing to fluctuate. Epilepsy surveillance systems show ictal and IEDs in circadian or multidien patterns. Regarding circadian fluctuation, they are facilitated by NREM sleep, but lighter stages more easily promote seizures[1 5 9 11 15 19]. During the REM sleep, the thalamocortical system responsible for the *suppression-burst firing*, spindles and slow waves is mainly favorable to absence epilepsy. The cholinergic arousal system provides tonic thalamocortical neuronal discharge flow for maintaining wake state, system commonly compromised in nocturnal frontal lobe epilepsy and arousal parasomnias, as suggested by Halász[10].

IEDs: Interictal Epileptiform Discharge; NREM: non-rapid eye movement, REM: rapid eye movement.

EPILEPSY AND SLEEP DISORDERS

Over the last many years, a new focus was given to clinical and pathophysiological aspects regarding epilepsy, and also the co-occurrence of sleep NREM-related parasomnias, in the entire sleep-wake spectrum. This happens mainly thanks tolong term intracerebral electrode implants that provide important electrophysiological information related to brain function during wakefulness and sleep[5] as happens with theNeuroVista in which subdural electrodes were chronically implanted in PWEs with intractable focal epilepsy. More data are given by The SeizureTracker.com, an online and mobile free service, seizure diary databases where the patients have focal or generalized epilepsy and include adults and children[14].

Comorbid sleep disorders are common in patients with sleep-related epilepsies which can negatively impact seizure control and quality of life [Nobili]. Sleep/wake disorders are 2-3 times more common in adult PWEs than in the general population, and these comorbidities are associated with a poorer quality of life and can also affect seizure control[8]. Particularly, in many cases, the treatment of sleep apnea reduces seizures[8]. In addition, the article published in the same issue of the Revista Brasileira de Neurologia deals with the symptoms of insomnia prevalent in PWEs with some questions about their underlying pathophysiology[7].

There is an interrelationship between the networks of sleep and epilepsy and also with those of cognitive functions[9 18]. The impairment of cognitive functions through sleep occurs especially in epileptic networks involving the thalamocortical system and the hippocampocortical memory encoding system[9]. Thus, an important link between epilepsy and sleep is the interference of epileptiform discharges with plastic functions in NREM sleep. This is the main reason for cognitive impairment in different forms of early epileptic encephalopathies that affect the brain at a special developmental window.

Better understanding and treatments aimed at this epilepsy-sleep relationship can improve the quality of life of PWEs. Early diagnosis and treatment of sleep disorders, especially respiratory disorders, are likely to be beneficial for seizure control[18].

The link between epilepsy and sleep is therefore close and reciprocal since any disturbance of sleep leads to an aggravation of seizures, and conversely, epileptic activity during sleep will result in sleep fragmentation, contributing to daytime sleepiness and impaired cognitive performance.

Seizures have sleep-wake and circadian patterns in several epilepsies and, in turn, alter sleep and circadian rhythms. The resulting sleep deprivation escalates the seizures that create a vicious cycle potentially leading to epilepsy-related progression or even death[15]. Besides, the circadian rhythms of cortisol may contribute to the timing of seizures, as they show similarities[8].

The sudden unexpected death in epilepsy (SUDEP) mechanism remains unclear but the role of sleep has been suspected, as the majority of the cases arise in sleep[4 8]. Changes in autonomic function during sleep increasing vulnerability to cardiorespiratory decompensation during a seizure may be a possible reason for the increased occurrence of SUDEP during sleep.

There are still no established procedures to evaluate patients with sleep-related epilepsies[18]. However, the identification and treatment of specific sleep disorders for the management and evolution of patients with sleep-related epilepsy is recommended[18].

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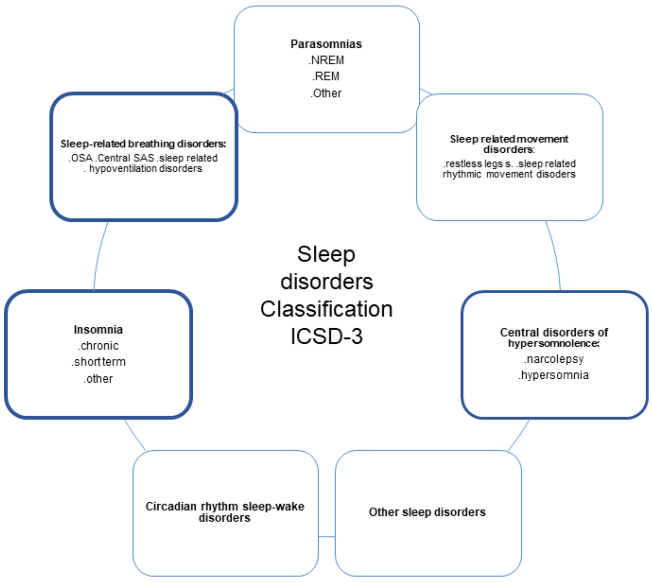

Figure 4. Sleep disorders according to ICSD-3. The most common sleep disorders in PCE are highlighted, such as insomnia, sleep-related breathing disorders and hypersomnolence disorders. However, although the latter group is characterized by excessive daytime sleepiness, common in PWEs, it does not include that derived from another sleep disorder such as sleep-related breathing or circadian rhythm abnormalities[20].

EPILEPSY MANAGEMENT AND MEDICATIONS

Treatment involves medications, lifestyle changes, besides others such as surgery and vagus nerve stimulation, when seizures are pharmacoresistant.

Self-regulation strategies, such as getting enough sleep, can play an important role in managing epilepsy.

If PWEs also have seizures at night, adaptations to the administration of antiepileptic drugs may be necessary, such as increasing the dose before bedtime, which may even favor a more restful sleep.

The side effects of these medications can vary, and some may cause drowsiness while others may make the patient more alert. However, their side effects are not clearly established, as shown in the systematic review by Jain and Glauser, apud Gomes[7].

In sum, sleep problems in PWEs are likely due more probably to a combination of factors, including the effects of nocturnal seizures, the side effects of antiepileptic medications, besides stress and anxiety.

The possibility to anticipate seizures would fit risk-stratified treatment strategies and behavioral modifications. Besides, chronic EEG recordings would allow pharmacologic treatments tailored to days of high seizure risk -here termed chronotherapy- and would help characterize long-timescale seizure dynamics to improve subsequent surgical planning. Chronotherapy would adjust to the PWEs according to their individuality, such as being "morning person" or "night owl"[19]. In conclusion, in this chronotherapy, drugs or neuromodulation could be administered in the circadian circuit or multidien peak of IEDs or seizures, as well as there could be the development of therapies against the exacerbation of seizures caused by sleep deprivation[15].

CONCLUSION

Sleep can affect seizures just as seizures can affect sleep, and for some PWEs, seizures will only happen during sleep, mainly related to it or only in the wake-up time. One of the hypotheses about the link between sleep and epileptic activity is how the electrical activity in different areas of the brain tends to be synchronized during NREM sleep. Excessive or hyper-synchronized synchronization can lead to seizures. Another hypothesis concerns physiological changes associated with circadian rhythms. Therefore, inquiring about sleep quality as well as screening, evaluation, and treatment for sleep disorders should be a part of care in PWEs.

Possibly, the improved understanding of the relationship between circadian rhythms, neuronal excitability and seizures will allow the recognition of new therapeutic targets for the treatment of sleep-related epilepsy, as well as more effective pharmacological and non-pharmacological regimens currently available[19]. This could break the vicious cycle of disease progression and reduce epilepsy-related mortality.

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