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Journal homepage: <https://www.ijashnb.org/>**Review Article****Review study on epileptiform discharge during sleep and circadian rhythm modulation during seizures**Sujithra Srinivas^{1,*}¹Healthcare Technology Innovation Center, Indian Institute of Technology–Madras, Chennai, Tamil Nadu, India**ARTICLE INFO***Article history:*

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ABSTRACT

Epilepsy is a neurological condition that affects approximately more than 50 million people around the globe^{1,2} out of which the prevalence of this disease is also seen in developed countries. Epilepsy can be clinical defined by two or more non triggered seizures. A seizure can be characterized as a paroxysmal event which is caused due to hyper-synchronization in the neurons that many have various reasons of manifestation.³ The neuronal discharge maybe focal spreading in specific brain cortex or widespread throughout the cortex. An Electroencephalogram (EEG) is used to in diagnosis and management of epilepsy and can be used for routine examinations, it also considered to be the golden standard investigation of epileptic syndrome.⁴ While using EEG the distribution, presence and frequency of interictal epileptiform discharges IEDs are suggestive diagnosis of epilepsy. In other words the presence of IEDs in an individual's EEG is a diagnosis of epilepsy.⁵ IEDs are predominantly found in EEG that is performed during sleep which can give basic diagnosis and prognosis of sleep related epilepsies in patients.⁶ During sleep latent interictal discharge are activated. Sleep IEDs are said to greatly affect the epilepsy management. These interaction mechanisms of sleep and epilepsies tends to bring about changes in behaviour of the seizure.

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The concept of interaction between sleep and epilepsy is not new and there have been evidences in the past there are seizures that appear only during sleep affecting the sleep characteristics.⁷ In major EEG finding the frequency, semiology and onset of the seizure is greatly influenced by sleep and sleep deprivation can trigger more unprovoked seizure. Some seizure types are said to have a unique circadian distributions and by understanding these patterns they can help in developing useful cues for diagnosis of seizures.⁸ Studies conducted by Gower in 1885 in 850 patients concluded that 20% seizures occurred at night which he called nocturnal, 40% seizures only during the day and called it Diurnal and 40% that occurred both at

day and night which was called diffuse.⁹ Another studies conducted at 1890 was analysing the time points at which the seizures occurred every day, the observations recorded seizure incident predominantly at nocturnal periods.⁹ In 1929 a group of scientist Russell Brain and Langdon used data from 66 patients over a period of 6 months analysed 2524 seizure recordings out of which 24% of the seizures were nocturnal, 76% occurred randomly at different time points.¹⁰ Janz in 1969 published his research work on chrono-type studies in tonic-conic seizures first described the term "awakening epilepsy" for seizure that appeared after sleep.¹¹ he recorded 2825 patients in which 27 % with both nocturnal and diurnal, 33% during wakefulness and 44% had seizures during sleep.^{11,12} It is known that interaction between sleep and epilepsy is a reciprocal relationship; while sleep affects the propagation of epilepsy and epileptic discharge in the brain is said to modify the

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sleep pattern and sleep fragmentations. Sleep deprivation is associated with many neurological disorders¹³ they are accompanied by several pathophysiological effects such as altered memory, loss of appetite and cognition.¹⁴

Although there are abundant of evidence that suggest sleep deprivation tends to facilitate the onset of epilepsy and the inter-ictal epileptiform discharges. On the contrary there are studies that propose an other critical view arguing that sleep deprivation is rarely associated with epilepsy and is more common symptoms of other neurological conditions such as depression and stress.¹⁴⁻¹⁶ The use of an Electroencephalograph EEG in understanding the bio signals of the brain revolutionized the concepts and understanding the relationship between epilepsy and sleep. IEDs were found common in NREM sleep than REM sleep staging.¹⁷ The frequency of occurrences of the epileptiform discharges during sleep is said to affect the sleep architecture.¹⁸ There are many focal and generalized epileptic syndromes that directly affect the sleep.¹⁷

1.1. Patho-physiology of sleep and epilepsy

In the recent years the research on understanding the patho-physiology of sleep and epilepsy has been giving greater interest but there is no clear understanding on explanation of the relationship between certain epilepsy types and its symptomatic presentation during sleep, awakening and drowsiness. Both in sleep and some generalized epilepsy syndromes share some common neuroanatomical presentations comprising of the limbic systems, specific thalamic nuclei and the ascending reticular activating systems. In many vitro electrophysiology studies using the human brain slices have presented the spontaneous responses and activity of synaptic activation in the hippocampal and neo cortex neurons can differ from normal and epileptic brain tissues.¹⁹ The inter-ictal epileptiform discharges is increased during NREM Non Rapid Eye Movement sleep and is lower during REM Rapid eye movement sleep, the IEDs can be both partial or generalized seizures.¹⁷ Animal studies conducted in cats by Sato and Nakashima presented that hippocampus trigger shows a lower incidence of electroconvulsive seizure in slow wave sleep when compared to wakefulness and REM sleep.¹⁷

It is hypothesized that there are many important mechanisms that are involved in the triggering of seizures during NREM sleep. The epileptic discharges can appear instead of sleep spindles in NREM sleep, that can be as a cortical response to the intrinsic thalamo cortical networks.¹⁹ The relation between production of sleep spindles and epileptic activity is a complex mechanism. Sleep spindle production happens In the fronto central areas due to its higher interconnectivity between each brain lobes, sleep is known to facilitate frontal seizure and motor seizure activities. EEG desynchronization and muscular tone can be seen in REM sleep. However the

EEG desynchronization stops the seizure from spreading in REM sleep and wakefulness and loss of muscle tone exempted its clinical expressions. Studies conducted earlier in humans and other higher mammalian species During REM activity have contributed more for the theory of reduced seizures during REM sleep. The following factors plays a crucial role in understand the seizures mechanisms. In REM sleep the increased GABA ergic activity is said to inhibit seizure propagation, there for REM sleep tends to have reduced seizure mechanisms other factors such as DE synchronization and reduced muscular tone contribute to further seizure inhibition.²⁰ The Biochemical changes that responsible for cerebral hypersynchrony can be seen in certain stages of sleep may lead to propagation of epileptic discharges. There are several other mechanisms has been implicated in this processes such as the loss of inhibition on some neuro circuitry, thalamo-cortical propagation and facilitation of epileptiform activity occurs in frontal lobe seizures. In the neuro circuitry, the participation of the acetylcholine system such as the Mono-aminergic and cholinergic brainstem receptors decreases the firing rates that causes a hyperpolarization in thalamo-cortical relay neurons which is predominant in NREM sleep stages. On the flipside in the REM sleep, cortical activation occurs through the cholinergic brainstem increases the neuronal firing rates causing a depolarization in the thalamo-cortex.¹⁹⁻²²

1.2. Sleep deprivation and interictal epileptiform activity

Sleep deprivation is an important trigger for increases of the interictal epileptiform activity in the brain; especially in the transition from wakefulness to light sleep which leads to increased cortical excitability.²³ Studies that used Transcranial magnetic stimulations have associated sleep deprivation with important changes that inhibits the balance of the primary motor cortex.²⁴ The primary motor cortex threshold can reflect the membrane excitability at the axon, thereby there is a calcium and sodium channel modulation. These modifications may be the reason for connection with the factors of the “activating” effects of sleep deprivation.²⁴ Some laboratory studies have used nitric oxide, as inhibitory substance of epileptic seizure.² In the present day nitric oxide is accepted to be more efficient in being a proconvulsant and anti convulsant neuromodulator.^{25,26} As discussed, there are many pathophysiological mechanisms that are linking sleep to epilepsy. Therefore, it is necessary to have a deep knowledge of the sleep characteristics is very essential for a proper understanding of the characteristics changes in different type of epileptic seizures.

1.3. Circadian rhythms and epilepsy

The current Knowledge about the circadian rhythm effects on epilepsy is very unclear and limited. Gaining knowledge

in understanding the factor is very important for the pathophysiology of epilepsy, for its diagnosis and treatment. The Circadian rhythms are endogenous and mediated by 24-hour cycles of several physiological processes that include the core body temperature, the sleep-wake cycle and hormone production. The circadian rhythms is modulated by the biological clock located in SCN suprachiasmatic nuclei. The retino-hypothalamic tract or pineal gland is responsible for the circadian pacemaker is called the process C, which causes alertness during the day, sleepiness during the night, and the increase in sleepiness is called the process S, which is dependent on the time awakening.²⁷ There are many studies using animal and human models that present the direct relationship between the sleep-wake Rhythm and epilepsy. Studies that involved rat models that were kept under constant darkness, presented spontaneous manifestation of limbic seizure that occurred on a circadian pattern.²⁸ In many studies it is shown that the loss of circadian transcription genes in mice can induce epilepsy in the models.²⁹ There are several examples associating the sleep and seizures in frontal lobe syndromes such as autosomal dominant nocturnal frontal lobe epilepsy And myoclonic seizures in juvenile myoclonic epilepsy the seizure likely appears in the awakening and last up to 10-15 mins longer. They present a circadian rhythmicity, appearing at specific time points of the day.³⁰ Several studies conducted at the past found that seizures appeared at specific time points following a circadian rhythmicity, irrespective of the origin of seizures. In temporal lobe the seizures were found mostly during the day. In extra temporal epilepsy the seizure presented are mostly nocturnal in nature.³⁰

The circadian activity patterns was monitored for two types of epileptic syndromes the juvenile myoclonic epilepsy and the temporal lobe epilepsy. The most interesting findings was that the juvenile myoclonic epilepsy group presented circadian characteristics of extreme evenings such as staying up late night and late awakening. While the temporal lobe epilepsy group presented modulated circadian characteristics with more likeliness towards morning³¹ Analysing many studies, we can see that the seizures follow a circadian rhythmicity irrespective of its origin in the brain. The temporal, parietal, and occipital lobes seizures occur mostly in the afternoon. While the seizures that originating in the frontal lobe occurs during the night. Other parameters like body temperature, hormonal levels and heart rate, have been recorded and studied.³² Many authors have reported that there is reduced heart rate variability in people with chronic epilepsy³³⁻⁴⁰ Likewise, the levels of cortisol have been described with postictal elevations, or elevated baseline prolactin levels are seen after seizure.³³ However, several studies have indicated the interaction of circadian rhythms and epilepsy. The evidences discussed suggest that physiological factors with a circadian distribution could influence the presentation

of many types of seizures.⁴¹

2. Conclusions

Despite many evidences of the relationship between sleep deprivation, sleep and epilepsy, we know very little about the mechanistic link between them.³⁸ The most recent research suggested the importance's and effects of the relationship in both sleep disorders and sleep deprivations can be a possible effect of excitatory neuronal functions which are found in certain types of sleep related epilepsy.³⁴ The tendency to present a circadian rhythmicity in some epileptic syndromes and the provoked effects of epileptic discharges in NREM sleep could be considered a good example.⁴⁰ However, many researcher question the claims, on the effects of sleep deprivation in epileptic populations is of a particular concern that needs to be substantiated.^{36,37,39} On the other hand chrono-therapy that can help in effectively treating sleep disorders can lead to an improved seizure control for epilepsy that occurs during sleep. By having the right understanding of the genesis, propagation of seizures in different brain regions and its effects on sleep and circadian rhythmicity of the seizure is crucial to bring out a correct diagnosis and proper treatment schedules.

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5. Conflict of Interest

The author declares that there is no conflict of interest.

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