Sleep and Epilepsy: A Complex Interplay

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Certain epilepsies are associated with sleep, especially in childhood, with epilepsies in adults activated by both sleep and sleep deprivation.

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Abstract

In this review we look to provide an overview of the complex interactions between sleep and epilepsy, and how knowledge of the interplay between the two can help in guiding management of disorders in both areas.

Introduction

Going as far back to ancient times, a relationship between sleep and epilepsy was recognized by the Greeks. Aristotle believed that altered states of consciousness, such as sleep or seizures, involved disassociation of the soul from the body, allowing prophecy of the future.[1] It was not until the late 1800s though that Gowers recognized that approximately 20% of those patients with epilepsy experience seizure solely in sleep. With the dawn of EEG, Gibbs recognized that epileptiform activity increased during sleep. It was recognized that close to half of patients with generalized tonic-clonic seizures had a nocturnal predominance. In this review, we seek to explore some of these relationships between epilepsy and sleep. Sometimes there can be problems differentiating between nocturnal seizures from sleep disorders. It is often important to recognize sleep's effects on epilepsy, along with comorbid sleep disorders affecting the treatment of epilepsy.

Sleep's effects on Epilepsy

There are two main sleep states, nonrapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep. Depending on the stage of sleep, epileptiform discharges can either be activated or inhibited. Typically epileptiform discharges are likely to propagate during NREM sleep along with traditional drowsy EEG arousal periods, as this is a more synchronized state, when we see such synchronized sleep architecture as sleep spindles and high amplitude delta waves. In contrast, during REM sleep, there are asynchronous cellular discharge patterns which make epileptic EEG potentials less likely to propagate. It has been seen that during NREM sleep, generalized epileptiform discharges are more frequent.[2] Generalized epileptiform discharges increase with deepening of non-REM sleep. These discharges can look irregular and focal at times in NREM sleep.[3] The differing stages of sleep also have an effect on focal epilepsy. NREM sleep has been shown to activate focal epileptiform abnormalities in patients with focal epilepsy, with more spikes seen during deeper stages of slow wave sleep compared to later stages of sleep.[4] Non-REM sleep is also associated with increased propagation of spikes with REM sleep more associated with a restriction of those abnormalities.[5] As a result, REM sleep can have helpful localizing

value for primary epileptogenic focus in temporal lobe epilepsy.[6] Interestingly enough, while interictal abnormalities are more prevalent in slow wave sleep, seizures tend to occur out of earlier stages of sleep more commonly.

Epilepsies Associated with Sleep

With epileptiform abnormalities being activated by certain stages of sleep, it is not unusual that there are certain types of epilepsies that occur more frequently out of sleep. There are multiple theories proposed to explain nocturnal seizures. As noted earlier, in NREM sleep seizures and interictal epileptiform abnormalities are activated, as this is a state of relative hypersynchronization, possibly leading to seizures. It has also been noted that arousals tend to activate certain types of epilepsies, such as juvenile myoclonic epilepsy, possibly pointing to the hyper synchronization during arousal was a cause for seizures. A third possibility points to circadian mechanisms playing a part in activating interictal epileptiform abnormalities. Several studies, including animal studies, have shown an afternoon or bimodal morning and afternoon peak for temporal lobe seizures, and evening peak for frontal lobe seizures.[7] Needless to say all these mechanisms might play a part in some of the sleep-related epilepsies. Many of the sleep-related epilepsies tend to start in childhood. In the pediatric population, one of the more common epilepsies is benign epilepsy of childhood with central temporal spikes, which has a characteristic EEG pattern and presents with focal motor seizures occurring during sleep.[8] About 70-80% of the seizures occur exclusively during sleep. Another common sleep related epilepsy seen in adolescence is Juvenile Myoclonic Epilepsy. Classically it presents with seizures upon awakening, and is associated with myoclonic jerks or generalized tonic-clonic seizures within 1-2 hours of awakening. A third type of sleep related epilepsy of childhood is Landau Kleffner syndrome. This epilepsy presents in childhood with language regression. On EEG there a continuous spike wave pattern during sleep, which is associated with cognitive and psychological deficits. In adults, focal onset seizures are the most common types of epilepsies occurring out of sleep. Of those, frontal and temporal lobe seizures are the most common types, with frontal lobe classically being the most common epilepsy to occur out of sleep. Classically nocturnal frontal lobe seizures are characterized by paroxysmal arousals with hyper motor movements with complex motor movements, lasting a brief amount of time. About half of the time the EEG is normal interictally, and can even be normal during the seizures. Sleep-related temporal lobe seizures are also quite frequent, representing one third of overall temporal lobe seizures in epilepsy monitoring units.[9] Many of these patients awaken from sleep with an aura, and then progress to their typical complex partial seizure, and have amnesia of the event.

Comorbid Sleep Disorders in Epilepsy

Patients with epilepsy can have comorbid sleep disorders. Excessive daytime sleepiness is a common complaint amongst epilepsy patients. Interestingly one study found little effect of the number of antiepileptic medications, seizure frequency, epilepsy syndrome, or nocturnal seizures on the complaint of excessive daytime sleepiness.[10] Sleep disordered breathing, such as obstructive sleep apnea, is thought to contribute to the excessive daytime sleepiness in some epilepsy patients. Approximately one third of patients undergoing epilepsy presurgical evaluation has been found to have sleep disordered breathing, with the most common one being obstructive sleep apnea.[11] Predisposing factors for obstructive sleep apnea include older age, male gender, obesity, and oropharyngeal narrowing, with an independent predictor in epilepsy being thickened neck circumference. Several retrospective studies have shown improved seizure control in patients with refractory epilepsy with continuous positive airway pressure treatment, with one study showing a comparable effect in some patients of adjunctive antiepileptic drug treatment; with 50-60% of patients experience a 50% or greater seizure reduction.[12] Insomnia can also affect patients with epilepsy. Arousals can be from a multiple factors, including epilepsy itself, medication effects, or other substance

abuse. Patients can also have fears associated with sleep, such as having a seizure out of sleep. Frequent arousals have been shown to be a trigger and manifestation of seizures themselves.[8] Patients with epilepsy have higher incidences of anxiety depression compared to the general population, with these disorders frequently being associated with insomnia.

Sleep Deprivation

Sleep deprivation has been classically associated with epileptic seizures and epileptiform discharges in patients.[13] Janz originally reported sleep deprivation or excessive alcohol precipitating the first seizure and 28 of 47 patients with juvenile myoclonic epilepsy. Sleep deprivation has also been shown to facilitate epileptiform discharges in patients with generalized epilepsy. However the question remains whether sleep deprivation has a genuine activating effect on epileptiform discharges, or acts as a way for sleep induction.[14] When comparing drug-induced sleep versus sleep deprivation-induced sleep, there is more epileptic discharges in activated patients with sleep deprivation versus drug-induced sleep. Awakening EEGs after sleep deprivation show more epileptiform discharges than sleep EEGs after sleep deprivation, suggesting that sleep deprivation as an independent activator of epileptiform discharges.

Effect of Epilepsy on Sleep

The effect of epilepsy on sleep can be related to the same pathophysiological mechanism causing epilepsy or to the effect of seizures or to the effect of antiepileptic therapy or a combination of these factors. Increase in sleep onset latency, increase in the wake time after sleep onset, increased instability of sleep stages, increased stage N1 and N2 NREM sleep (light sleep), decrease in sleep spindle density, and decrease in REM sleep have all been reported in patients with epilepsy. A seizure occurring out of sleep may be associated with decrease in REM sleep and sleep efficiency, and increase in light sleep. REM sleep and sleep efficiency may be further reduced if a seizure occurs before the first REM cycle.[15]

Many patients note postictal hypersomnolence following seizure which may last for more than a day at times.[16] Seizures can cause sleep disruption by decreasing sleep efficiency, increasing sleep stage shifts, and increasing periods of wakefulness in patients with primary generalized seizures or complex partial seizures compared with normal controls.[15] Increased sleep fragmentation and instability can happen on seizure-free nights as well.

Effect of Antiepileptic Drugs (AEDs) on Sleep

Antiepileptic drug, (AEDs) can cause sedation or may promote alertness and may have direct effect on sleep architecture. However, it is important to remember that it may be difficult to tease out the effect of AEDs on sleep from the effect of epilepsy itself. A review of studies describing the effects of AEDs on sleep reveals many aspects of effect of AEDs on sleep.[17] Phenytoin caused a decrease in sleep-onset latency. Phenobarbital and gabapentin reduced both sleep-onset latency and arousals from sleep. Increase in slow-wave sleep (SWS, N3 NREM sleep) was observed with pregabalin, carbamazepine and gabapentin whereas levetiracetam and ethosuximide caused a decrease. While ethosuximide and gabapentin potentiated REM sleep by increasing its duration, phenobarbital and phenytoin reduced REM sleep. Daytime sleepiness was not found to occur on topiramate, lamotrigine, zonisamide, and vigabatrin when tested by objective sleep measures like multiple sleep latency test (MSLT). Sleepiness may be associated with higher doses of phenobarbital, and possibly valproic acid and levetiracetam. Benzodiazepines increase NREM sleep but decrease SWS and sleep latency.[18] Increase in arousals has been reported with valproate.[19] Topiramate and zonisamide do not have significant effect on sleep architecture.[20,21] Lacosamide did not have any subjective or objective effect on sleep in healthy individuals.[22]

The effect of AEDs on sleep may vary from patient to patient. Therefore, patients should be closely monitored and questioned about changes in sleep patterns upon initiation or change in AED therapy. Knowledge of the effects of AEDs on sleep can help in medication selection based on the patient's sleep history. Patients with insomnia may benefit from being on an AED with higher sedating potential or a

higher dose of it in the evening. On the other hand, patients with hypersomnia or day-time sleepiness may benefit from being on an AED with less potential to cause sedation or one that promotes alertness in the morning.

Effect of Vagus Nerve Stimulation on Sleep

Studies looking at the effect of vagus nerve stimulation (VNS), a treatment modality in patients with medically refractory epilepsy, on sleep have shown variable results. Increased sleep latency on the MSLT indicating reduced day-time sleepiness was noted in patients on VNS therapy.[23] Patients with VNS therapy at relatively low stimulus intensities (output current of less than 1.5 mA) was found to have a significant improvement in sleep latency as observed on MSLT in another study.[24] Increased slow-wave sleep and stage NREM sleep in patients on VNS therapy have also been reported.[25] VNS has been associated with worsening of sleep-related breathing disorder in some cases, lowering the frequency and increasing the cycle time may be helpful to prevent worsening of sleep apnea during VNS therapy.[26]

Effect of Epilepsy Surgery on Sleep

Surgical treatment of epilepsy improves sleep in patients with epilepsy. A questionnaire based study to look at excessive daytime sleepiness and subjective sleep quality in patients who underwent epilepsy surgery for treatment of temporal lobe epilepsy (TLE) reported significant improvement in subjective sleep quality after epilepsy surgery.[27] Total sleep time and REM sleep significantly increased one year after TLE surgery associated with reduction in the frequency of seizures and interictal epileptiform discharges.[28]

Seizures and Parasomnias

Seizures occurring out of sleep can be difficult to distinguish from NREM- and REM-sleep related parasomnias. A clear description of the events is very important for differentiation between seizure and parasomnia but it may not always be available. Polysomnography with extended EEG montage may be necessary for a definitive diagnosis. NREM sleep parasomnias consisting of the disorders of arousal, which include sleep-walking, sleep terrors, and confusional arousals occur in the first-half or first-third of the night; they are typically associated with minimal or partial memory of the event. REM sleep behavior disorder is a REM sleep parasomnia characterized by patient's acting out their dreams due to absence of atonia during REM sleep; it is more common during the latter half of the night. Psychogenic nonepileptic spells (PNES) may occur during what appears to be behavioral sleep (pseudosleep) while EEG is consistent with wakefulness; eyes are typically closed during PNES whereas eyes are open during epileptic seizures. Epileptic seizures are characterized by their stereotypy, brief duration, amnesia for the event, and postical state with the caveat that consciousness may be intact and posticta state may be very brief with some frontal lobe onset seizures.

Sudden Unexpected Death in Epilepsy and Sleep

Sudden Unexpected Death in Epilepsy, (SUDEP), is defined as a "sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy with or without evidence for a seizure and excluding documented status epilepticus in which postmortem examination does not reveal a toxicologic or anatomic cause for death." The incidence may be as high as 6.0-9.3 per 1000 patient-years among patients evaluated for or treated with epilepsy surgery or those who continue to have seizures after epilepsy surgery.[29] The mechanism responsible for SUDEP remains unclear but the role of sleep has been suspected. In a Norwegian study 25 out of 42 patients were found dead in bed and 14 were thought to have died in sleep.[30] Several different mechanisms probably exist, and most research has focused on seizure related respiratory depression, cardiac arrhythmia, cerebral depression, and autonomic dysfunction.[29] Changes in autonomic function during sleep increasing vulnerability to cardiorespiratory decompensation during seizure may be a possible reason for increased occurrence of SUDEP during sleep.

Summary

In summary sleep and epilepsy are closely related, with certain stages of sleep providing a

hypersynchronous state, allowing more frequent epileptiform abnormalities, along with more frequent seizures. Certain epilepsies are associated with sleep, especially in childhood, with epilepsies in adults activated by both sleep and sleep deprivation. Comorbid sleep disorders are common in patients with epilepsy, and can affect epilepsy management. Sleep disorders are common and treatment of them especially sleep-disordered breathing may improve seizure control. Some parasomnias may mimic seizures – polysomnography with extended EEG montage may be necessary for characterization. Seizures can adversely affect quality and quantity of sleep whereas antiepileptic therapy (AEDs, VNS or surgery) can have negative or positive effect on sleep. Therefore, inquiring about sleep quality as well as screening, evaluation, and treatment for sleep disorders should be a part of care in patients with epilepsy.

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Disclosure

None reported. **MM**