

Sleep-related Epilepsy

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Sleep is important for the general health of all, but is particularly essential for individuals with epilepsy. In these patients, a complex relationship exists between seizures and sleep, and both must be considered for optimal care. In this review, recent advances in the field of epilepsy and sleep are considered. These include sleep disorders with a specific relationship to epilepsy, the influences of sleep and sleep deprivation on interictal epileptiform discharges, detrimental effects of seizures on sleep, and the effects (good and bad) of epilepsy treatments on sleep.

Introduction

Sleep dysfunction and sleep disorders are among the most common and the most underdiagnosed conditions in all of medicine, contributing to significant impairment in countless individuals, sometimes on a daily basis. Sleep-related dysfunction is particularly common in many types of neurologic dysfunction, including movement disorders such as Parkinson's disease, degenerative disorders such as Alzheimer's disease, and stroke. Perhaps no area, however, involves the number and diversity of interactions as exist between sleep and epilepsy.

Because epilepsy is in itself such a diverse disease, sleep may be an essential part of the syndrome (as in awakening grand mal epilepsy) or relatively unimportant. All types of seizures, however, have the potential for adverse effects on sleep. Additionally, medications used for epilepsy can in themselves affect sleep, sometimes adversely but in a few cases in a potentially beneficial manner.

The field of sleep-related epilepsy continues to evolve. This review highlights developments during the past year or so. A broader review of this area was recently published [1], as was an extensive textbook looking at all aspects of the field [2].

Sleep Disorders in Epilepsy Patients

Sleep disorders are common in the general population, so it is not surprising that they are also common in epilepsy

patients. The overall prevalence of sleep disorders in the epilepsy population was studied by Malow *et al.* [3]. When patients with epilepsy were compared with control patients using the Epworth Sleepiness Scale, epilepsy patients were drowsier. A difference was not seen, however, when a sleep apnea scale was included, emphasizing the importance of this condition. The study demonstrates that excessive daytime sleepiness is common in both epilepsy subjects and control subjects, and that much of this may be due to treatable conditions (particularly sleep apnea). In a retrospective study of 63 epilepsy patients who underwent polysomnography [4], the vast majority of patients (78%) were referred for obstructive sleep apnea, with others (46%) for excessive sleepiness, and a few (19%) for characterization of nocturnal spells. Studies diagnosed obstructive sleep apnea in 71% of referrals, most of whom were referred for that reason. Other diagnoses found were narcolepsy, insufficient sleep syndrome, and nocturnal seizures. Six patients had frequent periodic limb movements, but these were not clinically significant. In a similar investigation, Beran *et al.* [5] reviewed 50 patients with epilepsy referred to a sleep laboratory for all-night polysomnography. Fifty-four percent had sleep apnea, and 32% had periodic limb movements of sleep (six requiring medication). Of the 36 patients who were prescribed therapy based on the evaluation, six had significant improvement in seizures.

These studies emphasize the importance of sleep disorders in epilepsy patients. All show that sleep apnea is a particularly prevalent condition. There should, therefore, be a high suspicion of this condition in epilepsy patients, particularly as sleep apnea is known to exacerbate epileptic seizures [6,7].

Effect of Sleep on Interictal Discharges

Sleep and sleep-deprived electroencephalograms (EEGs) are commonly used diagnostically to increase the yield of epileptiform activity. Recording of overnight sleep improves the yield of interictal epileptiform discharges compared with routine daytime EEGs [8]. Sleep deprivation has been shown to independently activate epileptiform discharges independent of sleep duration or depth [9].

Specific increases in interictal spikes and sharp waves during slow wave sleep, with decreases during rapid eye movement (REM), were convincingly demonstrated by Sammaritano *et al.* [10]. An increase in spike frequency was also demonstrated with increasing delta power, a measure

of increasing sleep depth [11]. Interictal epileptiform discharges occurring during REM are less frequent; however, they can be particularly useful as these are more accurate for focus localization. When more than one epileptic focus is seen during wakefulness or non-REM sleep, discharges persisting during REM sleep are more likely the site of onset for the patient's seizures [10,12].

Nobili *et al.* [13] looked at a specific syndrome of sleep-related epilepsy, continuous spike waves during slow wave sleep, and correlated epileptiform activity with delta activity (a measure of delta sleep) and sigma activity (related to sleep spindles, and, therefore, to stage 2 sleep). These authors found that epileptiform activity was increased in lighter non-REM (stage 2), decreased in slow wave (delta) sleep, and severely decreased in REM. This shows that interictal activity in different syndromes may have distinct associations with sleep, as the decreases shown here during slow wave sleep are clearly different than increases seen with partial epilepsy. REM sleep, however, appears to decrease interictal activity in all conditions.

Specific Syndromes and Their Relationship to Epilepsy

Frontal lobe epilepsies are a frequent diagnostic dilemma for a number of reasons. The seizures are frequently unwitnessed and semiology is often bizarre. Prominent choking and abnormal motor activity can lead to a misdiagnosis of sleep apnea [14] or other sleep disturbance [15]. In a review of 100 consecutive cases of nocturnal frontal lobe epilepsy [16], 28% occurred in sleep stages 3 or 4, and only 3% during REM. Clear epileptiform abnormalities on routine EEG occurred in less than half of patients. Forty-two patients showed a clear ictal discharge on polysomnography. Autosomal dominant nocturnal frontal lobe epilepsy is characterized by enuresis, sudden awakenings with dystonic or dyskinetic movements, complex behavior, and violent behavior in sleep [17]. Most patients showed ictal or rhythmic activity over the frontal region. Autosomal dominant inheritance with reduced penetrance was seen in most, but another study [18] showed heterogeneity. Llandau-Kleffner syndrome (LKS) is a condition of acquired aphasia, frequently (but not always) with epileptic seizures and a markedly epileptiform EEG, particularly in sleep. O'Regan *et al.* [19] studied 25 children with an acquired disorder of communication and seizures, but not strictly meeting criteria for LKS. EEGs were uniformly epileptiform, usually (16 of 25 patients) worsening with sleep. Magnetic resonance imaging (MRI) was typically normal, but single photon emission computed tomography (SPECT) was abnormal (22 of 25 patients). Most were considered to have a receptive aphasia. Language deficits have been hypothesized to result from the persistent epileptic discharges, as evidenced by hypometabolism on SPECT [19].

Absence epilepsy is generally a benign condition, with remission occurring during adolescence. Guye *et al.* [20] reviewed 31 cases of absence epilepsy and looked for the presence of fast (10 to 15 Hz) discharges during slow wave sleep. This pattern has been associated with the Lennox-Gastaut syndrome [21]. In the four absence patients identified with this pattern who were followed to adulthood (aged 34 years or over), all had persistent absence and generalized tonic-clonic seizures. This suggests that absence patients with fast discharges during slow wave sleep may constitute a group at risk for seizures persisting into adulthood.

Certain types of seizures are known to have a circadian pattern such as awakening grand mal epilepsy. A number of studies have looked into the possibility that focal seizures have specific patterns of occurrence as well. Rats with a model of limbic epilepsy and humans with medial temporal or extratemporal seizures show increasing seizures during daylight hours [22]. This suggests that there is a diurnal pattern to temporal lobe epilepsy; however it is puzzling that a predominantly nocturnal animal, the rat, and diurnal humans both showed increased seizures during daylight hours.

Clinically, it is fairly well accepted that seizures due to frontal lobe localization-related epilepsy tend to occur more frequently during sleep. Three studies in patients with epilepsy patients support that frontal lobe seizures occur more frequently during sleep compared with temporal lobe seizures [23,24,25•]. Seizures that occur exclusively during sleep may represent a subset with an excellent prognosis compared with seizures that occur in both sleep and wakefulness [26,27].

One of the most interesting and robust findings across many studies is the relative protection of REM against the occurrence of focal seizures. In rats, administration of a substance that enhances REM activity (carbachol) also increases the threshold current required to produce an afterdischarge in the amygdala [28]. Several studies in epilepsy patients suggest that seizures are rare during REM [24,25•,28]. In a retrospective study of 14 patients with temporal lobe epilepsy, seizures occurred most frequently during non-REM sleep and specifically preceding arousals [29]. A recent prospective analysis of seizures recorded in an epilepsy monitoring unit has confirmed these findings [25•]. This study had the advantage of prospective design, inclusion of eye and chin electromyogram leads for sleep scoring, and polysomnography in a subset of patients. This analysis of 613 seizures in 133 patients showed that seizures begin commonly during the lighter stages of non-REM sleep, but are rare during slow wave sleep; none were recorded that began during REM. Temporal lobe partial seizures, but not frontal lobe seizures, were more likely to generalize when beginning during sleep compared with wakefulness, a finding that was also seen in a previous retrospective study [24].

Table 1. Parasomnias commonly mistaken for epilepsy

Occur during wakefulness	Occur during non-REM sleep	Occur during REM sleep
Sleep attacks Cataplexy	Night terror Somnambulism Sleep enuresis Periodic limb movements/restless legs syndrome	Hypnagogic hallucinations Sleep paralysis REM behavior disorder

REM—rapid eye movement.

It is not clear how the REM state could inhibit the occurrence of seizures or (in the case of temporal lobe seizures) reduce the rate of secondary generalization. Electrophysiologically, cerebral activity during REM most closely resembles wakefulness or light sleep; however the previous studies show that seizures occur less frequently during REM than either of these states. It may be that relative hypersynchrony present during non-REM sleep may facilitate onset and/or spread of certain partial seizures. This is an important area for future research, as understanding the mechanism whereby REM sleep inhibits seizure onset and propagation could lead to novel treatments for intractable epilepsy.

The relationship of sleep deprivation to seizure occurrence was examined by Malow *et al.* [30]. Most clinicians believe that sleep deprivation will increase the occurrence of most (if not all) seizure types. These authors performed a controlled study of patients with refractory epilepsy in an epilepsy monitoring unit, where patients were randomized to either sleep deprivation every other night or no sleep deprivation, and found that the sleep-deprived patients did not have seizures sooner. It could not be distinguished from this study whether specific subtypes of partial or other seizure types are more sensitive to this maneuver.

Diagnostic Issues

As both epilepsy and many parasomnias are paroxysmal events associated with behavioral changes, there is frequently diagnostic confusion between the two. Common parasomnias mistaken for epilepsy are summarized in Table 1. Also like seizures, parasomnias are rarely (if ever) witnessed by the physician, and diagnosis depends on history from patients and onlookers. Because parasomnias usually occur at night, onlookers frequently do not see the onset of the episode. The parasomnias most commonly confused with epilepsy are confusional arousals, cataplexy, and REM behavior disorder.

When the diagnosis is in question, either video-EEG monitoring or polysomnography are appropriate. Video

EEG has the advantage of a much more extensive coverage of EEG on routine studies. Modern polysomnographic equipment can typically accommodate additional EEG electrodes when appropriate, but this should be made clear to the laboratory when scheduling the patient. In a few centers, polysomnography and video-EEG can be performed simultaneously, therefore, allowing a complete evaluation in very complicated patients. This is particularly important when seizure disorders coexist with sleep disorders in the same patient. A recent review of this area was written by Dyken *et al.* [31•].

Effects of Seizures and the Epileptic Condition on Sleep

Epilepsy and epileptic seizures could influence the structure of sleep in several ways, including the appearance of normal sleep discharges (spindles and K-complexes) and the pattern and proportion of sleep stages through the night. In general, it is thought that focal lesions, including localization-related epilepsy, can result in inhibition of sleep spindles on the affected side. Using a retrospective analysis of EEGs from patients without brain pathology, Clemens and Menes [32] found that patients with idiopathic generalized epilepsy had no spindle lateralization; however, those with localization-related epilepsy had enhancement of spindles ipsilateral to seizure onset zone.

In a polysomnographic study of epilepsy patients without seizures [23], there were no differences in percentage in each sleep stage between frontal and temporal lobe epilepsy patients or between either group and control subjects. Temporal lobe patients showed increased wakefulness after sleep onset compared with frontal lobe patients and, therefore, decreased sleep efficiency.

The specific effects of temporal lobe seizures on sleep structure were examined by Bazil *et al.* [33•]. When patients with temporal lobe epilepsy were compared under baseline conditions (seizure free) and following daytime complex partial or secondarily generalized seizures, there was a significant decrease in REM the following night without significant changes in other sleep stages or in sleep efficiency. When seizures occurred at night, this decrease in REM was more pronounced (16% vs 7%), and there were increases in stage 1 and decreases in sleep efficiency. Perhaps not surprisingly, a report of sleep following partial status epilepticus showed severe inhibition of REM sleep for several days [34]. All of these studies show that partial seizures have the capacity for long-term disruption of normal sleep, particularly REM, which lasts at least through the following night and (in the case of status epilepticus) often for several days. This may help explain why many patients with seizures report difficulty functioning the following day, particularly with nocturnal seizures.

Table 2. Effects of antiepileptic drugs on sleep parameters

Drug	Daytime drowsiness	Sleep latency	Stage I	SWS	REM
Barbituates	Worsens	Improves	No effect	Worsens	Worsens
Benzodiazepines	Worsens	Improves	No effect	Worsens	Worsens
Carbamazepine	Worsens	No effect	No effect	No effect	Worsens/no effect
Phenytoin	Worsens	Improves	No effect	No effect	Worsens
Valproic acid	Worsens	No effect	Worsens	No effect	No effect
Gabapentin	Unknown	No effect	No effect	Improves	Improves/no effect
Felbamate	Unknown	Unknown	Unknown	Unknown	Unknown
Lamotrigine	No effect	No effect	No effect	Improves/worsens	Improves/no effect
Levetiracetam	Unknown	Unknown	No effect	No effect	Improves
Oxcarbazepine	Unknown	Unknown	Unknown	Unknown	Unknown
Tiagabine	Unknown	Unknown	Unknown	Unknown	Unknown
Topiramate	Unknown	Unknown	Unknown	Unknown	Unknown
Zonisamide	Unknown	Unknown	Unknown	Unknown	Unknown

REM—rapid eye movement; SWS—slow wave sleep.

Effects of Anticonvulsant Drugs on Sleep

Studies looking at the effects of anticonvulsant medications on sleep must be interpreted with caution. As seizures are known to affect sleep, addition of anticonvulsant medications may improve sleep through improved seizure control [15]. When medications are used in polytherapy, there may be pharmacokinetic or pharmacodynamic interactions affecting sleep. Studies in normal subjects would control for these variables; however, they have not been performed with most medications. Even so, it is possible that anticonvulsants would have differential effects on patients with epilepsy, independent of seizures. Placebo-controlled studies in patients with epilepsy, although perhaps useful from a scientific standpoint, would place patients at risk for seizures, and these seizures would further confound the results.

Despite these limitations, there is a fair amount known about various anticonvulsants in epilepsy patients. Drowsiness is increased in patients taking carbamazepine, phenytoin, valproic acid, and phenobarbital by the maintenance of wakefulness test [35], although this study could not distinguish between the drugs. Many agents have been reported to depress REM sleep, including phenobarbital [36–38], phenytoin [36,39–41], and carbamazepine [40,42•,43]. Decreased REM may not be present when carbamazepine is used chronically [42•,44]. Studies of valproate have shown either no effect on sleep [39,45] or mild sleep disruption manifested by increased stage 1 sleep [46].

Sleep studies of some newer anticonvulsants have been performed recently. One study of lamotrigine as add-on therapy showed an increase in REM [42•], but these patients (probably because of concomitant antiepileptic drugs) had relatively low amounts of REM at baseline. In a more rigorously controlled add-on study of lamotrigine, 10 patients with focal epilepsy who were taking either carbamazepine or phenytoin had lamotrig-

ine added [47•]. Ambulatory polysomnography was performed before and after the addition of lamotrigine. These authors showed a significant decrease in slow wave sleep with lamotrigine; there was an increase in stage 2 sleep, and all other parameters (including REM) were unchanged. There was slight improvement in phase shifts and arousal index, although these were not significant. Subjective sleep indices showed no change with treatment. This study has the distinct advantage of comparing patients with themselves; it has the disadvantage of being unblinded and an add-on treatment.

Gabapentin has been shown to increase slow wave sleep as monotherapy [46,48] and as add-on therapy [42•]. REM was increased in one study [42•]. A report of levetiracetam in monotherapy showed no significant changes compared with similar patients on no drug, although an increase in REM was seen [49]. In a single small study in normal, elderly subjects, tiagabine increased sleep efficiency and slow wave sleep [50]. Studies of felbamate, oxcarbazepine, zonisamide, tiagabine, and topiramate have not previously been published. The effects of various antiepileptic drugs on sleep parameters are summarized in Table 2.

Effects of the Vagus Nerve Stimulator on Sleep

The vagus nerve stimulator is now approved for treatment of refractory seizures. As projections from the vagus nerve undoubtedly stimulate brainstem structures, some of which are related to sleep and alertness, it is possible that this device has independent effects on sleep and wakefulness. Malow *et al.* [51•] studied 16 patients with refractory epilepsy before and after vagus nerve stimulator implantation, using polysomnography, multiple sleep latency tests, and the Epworth Sleepiness Scale. There was no change in polysomnographic sleep parameters following treatment;

however, there was significant improvement in alertness with the device as measured by both multiple sleep latency test and the Epworth Sleepiness Scale. In a subset of patients, however, the vagus nerve stimulator can worsen obstructive sleep apnea [52].

Melatonin and Epilepsy

Melatonin is a sleep-related hormone that is particularly important in regulating circadian rhythms. There is preliminary evidence from a number of small trials that exogenous melatonin can improve seizures in animal models of epilepsy [53] and in humans [54]. It is unclear from these studies whether there is a direct anticonvulsant effect or whether there is improvement through sleep-related parameters. Bazil *et al.* [55•] measured salivary melatonin in patients with intractable temporal lobe epilepsy both with and without seizures, and compared this with normal control patients. They found that patients with epilepsy had significantly lower baseline levels of melatonin compared with control subjects, but this increased dramatically following seizures. If melatonin is in fact an endogenous anticonvulsant, decreased levels in these patients could be contributing to intractability.

Conclusions

Interactions between sleep and epilepsy are important for the care of epilepsy patients on many levels. Diagnostically, the usefulness of sleep and sleep-deprived recordings in the complete characterization of patients is well demonstrated. Relationship of seizures to sleep and wakefulness can help in classifying epilepsy syndromes and in prognosis. Seizures clearly interfere with quality of life even when restricted to sleep, most likely through the severe disruption of normal sleep patterns known to occur. Although exclusively or predominantly nocturnal seizures may be less disruptive to patients on certain levels, their elimination should still be a primary goal. Finally, the choice of treatment (anticonvulsant or vagus nerve stimulator) can affect sleep, and this is an important consideration in the total care of the patient with epilepsy.

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