

Epilepsy and Sleep Disorders

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Abstract

There is a close association between sleep and epilepsy. In some epilepsy syndromes, seizures occur predominantly (or even exclusively) during sleep or on awakening. Excessive daytime sleepiness is common in patients with epilepsy and may be due not only to medication but also to nocturnal seizures or concomitant sleep disorders. Sleep disorders such as obstructive sleep apnea can worsen epilepsy, with improvement of seizure control following appropriate treatment of the sleep disorder. Conversely, epilepsy and antiepileptic medication can worsen sleep disorders. Nocturnal epileptic seizures may be difficult to differentiate from parasomnias, in particular non-rapid eye movement parasomnias such as night terrors, sleepwalking and confusional arousals, on history alone since there are semiologic similarities between the two disorders. Schemes have been developed to facilitate differential diagnosis, although this remains a challenge even using the gold standard, video-electroencephalography telemetry.

Keywords

Frontal lobe epilepsy, nocturnal seizures, non-rapid eye movement parasomnia, sleep apnea, sleepwalking, night terrors

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Throughout the ages, sleep has been considered akin to death; indeed, Homer referred to sleep as the 'brother of death'. However, the advent of electroencephalography (EEG) has expelled this misconception and sleep is now recognized as consisting of active brain states during which many biologic processes occur, such as synaptic plasticity and memory consolidation.¹ Sleep can be broadly divided into rapid eye movement (REM) sleep and non-REM (NREM) sleep. These sleep states cycle over 90 minutes throughout the night. NREM can be subdivided into light (stages I/II) and deep (stages III/IV) sleep (see *Figure 1*). As sleep progresses, deep sleep periods become shorter and are absent towards the morning; conversely, REM sleep time increases.² Since different conditions occur in different sleep stages/states, the timing of events during the night is important for diagnosis. Epilepsy and sleep have an important temporal association and can interact (i.e. lack of sleep can precipitate seizures and seizures can disrupt sleep). Moreover, nocturnal epileptic seizures can be misdiagnosed as sleep disorders and vice versa.

Temporal Association of Epilepsy with Sleep

Perhaps the best established relationship between epilepsy syndromes and sleep is in idiopathic generalized epilepsy syndromes, in which seizures occur shortly after waking. This is especially evident in the myoclonic jerks and tonic-clonic seizures in juvenile myoclonic epilepsy.³ It is also striking that, in some people, seizures can occur exclusively at night, an observation mentioned in ancient texts. Indeed, Aristotle stated that "the beginning of this malady (epilepsy) takes place

with many during sleep, and their subsequent habitual seizures occur in sleep, not in waking hours".⁴ Later studies from the 19th and early 20th centuries determined that 20 % of patients with epilepsy have nocturnal seizures only.^{5,6} Importantly, the occurrence of seizures predominantly during sleep is a characteristic of specific epilepsy syndromes. In particular, nocturnal seizures are typical of frontal lobe epilepsy, in which seizures usually cluster and can occur many times in a night.⁷ Nocturnal seizures occur throughout all stages of NREM sleep and are distributed proportionately, so that they occur more frequently during light stages rather than deep stages (see *Figure 2*).^{8,9} Similarly, seizures in benign focal epilepsy with centrotemporal spikes (BECTS) show a predilection for sleep or drowsiness.¹⁰ Although temporal lobe epilepsy does not show this diurnal variation, if temporal lobe seizures occur during the night, they are more likely to be secondary generalized.^{7,9}

Certain epileptic encephalopathies also show marked diurnal variation in seizure manifestation and electrographic activity. This is a particular feature of electrical status epilepticus during sleep (ESES), which is characterized by spike and wave discharges in 85–100% of NREM sleep.¹¹ ESES is associated with certain epilepsy syndromes, including Landau-Kleffner syndrome, Lennox-Gastaut syndrome, continuous spikes and waves during sleep and benign epilepsy of childhood with rolandic spikes, and is associated with autistic/language regression. Interictal epileptiform discharges (IEDs) on the EEG increase with depth

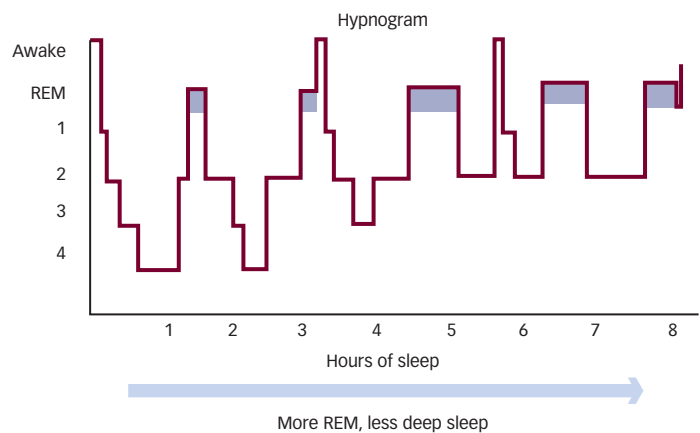
of NREM sleep and are often seen over a wider field than IEDs occurring during wakefulness.^{12,13} Sleep spindles and K complexes are generated in similar circuits to those involved in the generation of spike-wave discharges in generalized epilepsies¹⁴ (however, this relationship may be more complex);¹⁵ this may explain the association of spike-wave discharges with these sleep phenomena. Seizures and epileptiform abnormalities are more commonly seen in transition between sleep stages and also during periods of sleep instability. Indeed, it has been suggested that the increase in spike-wave activity seen after sleep deprivation may be due to more frequent fluctuations in vigilance levels during both wakefulness and sleep.¹⁶ The cyclical alternating patterns (CAPs) seen during NREM sleep have been proposed to be a measure of both changes in sleep states and sleep instability.¹⁷ In primary generalized and some focal epilepsies (although probably not benign epilepsy with rolandic spikes), interictal discharges are most frequent during CAP phase A than CAP phase B or non-CAP sleep.^{16,17}

Interaction of Sleep and Seizures

Excessive daytime somnolence (EDS) is commonplace in patients with epilepsy¹⁸ and has often been attributed to antiepileptic medication or seizures. Indeed, unrecognized nocturnal seizures can present as daytime somnolence.¹⁹ Moreover, patients with more frequent seizures are more likely to report sleep disturbance than control subjects or patients with less frequent seizures, regardless of epilepsy syndrome.¹⁸ Patients with epilepsy have an increased number of awakenings during the night and a reduction or fragmentation of REM sleep.²⁰ Seizures and frequent interictal epileptiform activity can also change sleep architecture, causing more unstable sleep periods as measured with CAPs in both partial and generalized epilepsies.²¹ Polysomnography following complex partial seizures has revealed a reduced amount of REM sleep after seizures.²⁰ This effect was most pronounced after nocturnal seizures (from 16 to 7 %), but was also significant after seizures occurring the previous day (from 18 to 12 %). Nocturnal seizures also reduced the amount of stage II and IV sleep and increased the amount of stage I sleep.²⁰ This was associated with reduced sleep efficiency and increased drowsiness the day after.

However, the major causes of sleepiness in people with epilepsy are co-morbidities such as periodic limb movements and, in particular, sleep apnea.²² Obstructive sleep apnea (OSA) is over-represented in people with epilepsy, occurring in 10 % of people with epilepsy without other neurologic or systemic disease.²³ OSA is even more frequent in people with refractory epilepsy and has been reported in one-third of patients (of whom over one-third have moderate to severe OSA) investigated for epilepsy surgery.²⁴ The risk factors for obstructive sleep apnea are the same as in the general population: older age, male gender and obesity.²³ OSA fragments sleep and reduces sleep time, which can have a detrimental effect on seizure control. In older adults with late-onset seizures or worsening of seizure control, OSA is associated with seizure exacerbations.²⁵ Several studies have also shown an improvement of seizure control after treatment of concomitant OSA.^{22,26-29} In a recent pilot study in patients with refractory epilepsy and OSA, a 50 % reduction in seizures was observed in 28 % of treated patients versus 15 % of patients in the sham group. Four of 22 patients receiving continuous positive airway pressure (CPAP) treatment and one of 13 receiving sham treatment became seizure-free.²⁷

Figure 1: Typical Hypnogram Showing Sleep Stages Through the Night



As the night progresses so there is less stage 3/4 sleep and a greater proportion of REM sleep. REM = rapid eye movement.

Table 1: Effects of Some Antiepileptic Drugs on Sleep

	Sleep Efficiency	Stage 1	Stage 2	Deep Sleep	REM	Arousal
PB	+		+	0	-	-
PHT	0	+	+	-	0	0
CBZ	0	0	0	0	0	0
VPA	+		-	0	0	0
GBP	0	0	0	+	+	-
LTG	0	0	+	-	+	-
TPM	0	0	0	0	0	0

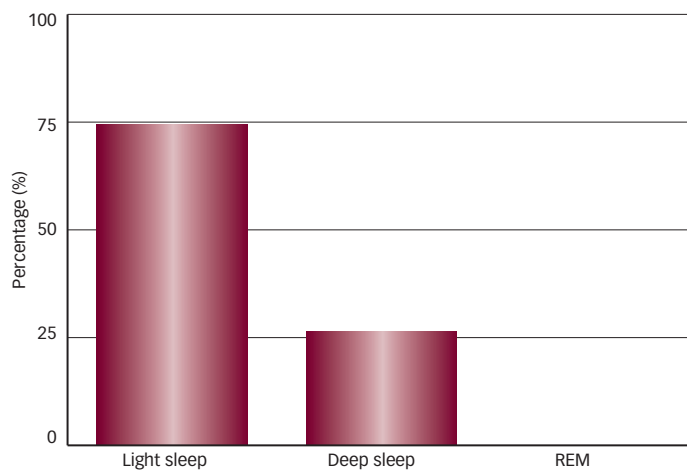
- = decrease; + = increase; 0 = no change; CBZ = carbamazepine; GBP = gabapentin; LTG = lamotrigine; PB = phenobarbitone; PHT = phenytoin; REM = rapid eye movement; TPM = topiramate; VPA = valproate. Green represents sleep promotion, while red represents sleep disruption.

Epilepsy and antiepileptic drugs may also aggravate OSA. Remission of OSA as well as seizures has been reported in a patient following frontal lobe resection.³⁰ Seizures themselves can result in apnea both ictally and, importantly, post-ictally.³¹ Furthermore, an increase in apnea-hypopnea index has been seen after nocturnal frontal lobe seizures in a patient with epilepsy and mild OSA.³² Antiepileptic drugs can also worsen OSA through sedation, muscle relaxation and weight gain. Non-pharmacologic treatment for epilepsy with vagus nerve stimulation has also been shown to worsen OSA.³³ Identification and treatment of both epilepsy and OSA are hence important to optimize patient outcome. Antiepileptic drugs can also have a complex effect on sleep and different drugs can have very varied effects on sleep quality and quantity, ranging from hypersomnolence to insomnia (see Table 1).³⁴

Nocturnal Frontal Lobe Epilepsy and Non-rapid Eye Movement Parasomnia Diagnosis and Differential Diagnosis

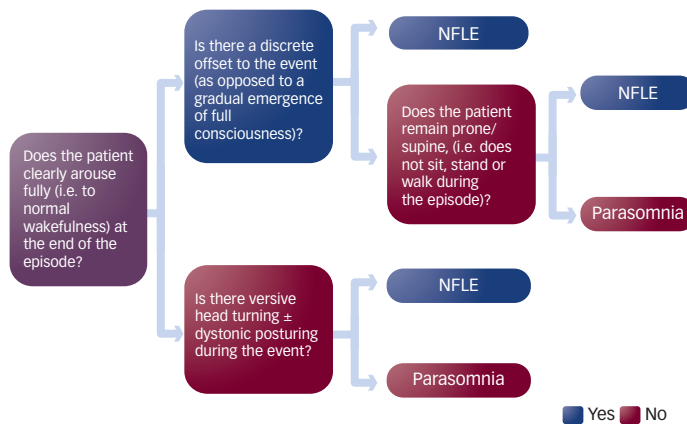
Nocturnal frontal lobe seizures can manifest as paroxysmal arousals, which consist of brief, sudden eye opening, head raising or sitting up in bed, a frightened expression and, sometimes, vocalization; or nocturnal paroxysmal dystonia, which involves dystonic posturing and hypermotor (complex motor) phenomena, and episodic nocturnal wanderings, which are longer in duration (one to three minutes), with associated stereotyped

Figure 2: In What Sleep Stage do Seizures Occur?



The majority occur during light sleep (proportionate to the amount of light sleep in a night). Seizures rarely occur during REM sleep. REM = rapid eye movement. Source: Sinha et al., 2006.⁷

Figure 3: Scheme for Differentiating Non-rapid Eye Movement Parasomnia from Nocturnal Frontal Lobe Epilepsy



NFLE = nocturnal frontal lobe epilepsy. Source: Derry et al., 2009.⁴¹

dystonic movements.³⁵ People with nocturnal frontal lobe epilepsy (NFLE) will commonly have more than one of these seizure types. Daytime interictal EEG shows epileptiform abnormalities in up to one-third of cases; this increases to 50 % of nocturnal EEGs.³⁵ Ictal EEG is often unhelpful or there may be only subtle features such as electrodecrement or rhythmic frontal slow.³⁵ Tachycardia is common during the seizures.³⁵ Although it can be difficult to differentiate epileptic arousals from physiologic arousals, sleep usually lightens after epileptic arousals, while people often return to the same sleep stage with brief physiologic arousals/movements. Seizures cluster and occur throughout the night, often many times per night.

NREM parasomnias usually occur from deep sleep.³⁶ There are three main subtypes of NREM parasomnia: sleepwalking (somnambulism), night terrors (pavor nocturnis) and confusional arousal. Certain people seem predisposed to having NREM parasomnia and there is often a family

history.³⁶ NREM parasomnia can be precipitated by sleep deprivation, stress and other sleep disorders (e.g. sleep apnea). People are invariably confused during the event, and are usually amnesic for the event. These conditions are most common in children, but do occur in adults. They occur usually one to three times per night and mostly in the first third of the night (when deep sleep is occurring).³⁶ Sleepwalking is characterized by wanderings, often with associated complex behaviors such as carrying objects and eating. The episode usually lasts a matter of minutes. Night terrors are characterized by screaming and prominent sympathetic nervous system activity (tachycardia, mydriasis and excessive sweating). If woken from these, people will often recall dream mentation that usually lacks a narrative structure and consists of escaping from something or someone. Confusional arousals consist of episodes of confusion arising from sleep, about which the person is usually amnesic.

NREM parasomnias and epilepsy can sometimes be difficult to distinguish, especially on history alone. Furthermore, they can co-exist in the same subject. There is an unusually high proportion of patients with NFLE reporting a history of parasomnias—34 % in one survey.³⁵ This could tentatively be due to nocturnal epileptic seizures erroneously being diagnosed as parasomnias in childhood and only when episodes continue later in life being correctly diagnosed as epileptic seizures, or it could be the precipitation of NREM parasomnias by disruption of sleep by seizures. However, a recent study has confirmed an increased frequency of arousal parasomnias in families with NFLE compared with control subjects, supporting the hypothesis that there could be a link between the two involving abnormal arousal systems.³⁷

The similarities between features seen during NFLE and parasomnias have prompted the hypothesis that the disorders may have a common pathogenic background.³⁸ This builds on MacLean's idea of the triune brain: neomammalian brain (neocortex), paleomammalian brain (limbic system) and reptilian brain (basal ganglia).³⁹ Normally, central pattern generators (CPGs), neuronal networks activating specific sequences of motor responses in the paleomammalian and reptilian brain, are controlled by the neomammalian brain. However, sleep or epilepsy remove this control (inhibiting the neocortex) and, facilitated by arousal, this results in the emergence of stereotyped inborn fixed action patterns.³⁸ Such release phenomena include oroalimentary automatisms, bruxism, pedalling activity, wanderings and emotional responses (ictal fear, sleep terrors).⁴⁰ In support of this theory is the observation that minor motor events associated with frontal lobe epilepsy are often not directly associated with epileptiform discharges, raising the possibility that their genesis is due to the non-specific triggering of CPGs by either epileptiform discharges or fluctuations in arousal, or even that epileptiform discharges induce minor motor events by provoking an arousal.^{38,40} Indeed, a seizure discharge could act as an internal arousal stimulus and its effect would therefore be similar to that of an intrinsic (snore, cough) or extrinsic (noise) physiologic stimulus. This results in non-specific arousal behavior that does not depend on the nature of the stimulus.⁴¹

Is there any way of clearly distinguishing nocturnal frontal lobe seizures from parasomnias? If they are very brief, it can be particularly difficult. However, distinguishing on the basis of frequency, time of night and stage of sleep can be particularly useful. Furthermore, there are

semiologic features that can help distinguish the two.⁴¹ Importantly, brevity, sitting, standing/walking, preceding arousal or fearful emotional behaviour are not good differentiators. Stereotypy and dystonic posturing are more common features in seizures, while yawning, waxing and waning, prolonged duration (over two minutes) and indistinct offset are more common in parasomnias.⁴¹ This last feature is quite a notable difference between seizures and NREM parasomnias on video. A scheme has been devised by Derry and co-workers that can differentiate the majority of seizures and parasomnia (see *Figure 3*).⁴¹ Nevertheless, even with access to good-quality video-EEG telemetry, the differentiation can be difficult and there is often disagreement between experts who are shown the same videos.⁴²

Conclusion

There is a close association between sleep and epilepsy. Importantly, sleep disorders can worsen epilepsy control and treatment of these disorders (e.g. CPAP for sleep apnea) can improve epilepsy control. Conversely, epilepsy and antiepileptic drugs can disrupt sleep, leading to daytime somnolence. Perhaps one of the greatest challenges is in the diagnosis of nocturnal events, in particular the differentiation of NREM parasomnias from nocturnal seizures. Since the eyewitness accounts of these events are often poor, video-EEG telemetry is frequently required. However, minor events, whether caused by arousal or epileptic activity, can have very similar semiologies. EEG is often unhelpful and it can be difficult even with video-EEG telemetry to diagnose these events with certainty. ■

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