Sleep and Epilepsy

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Since Aristotle and Hippocrates noted the occurrence of epileptic seizures during sleep, the relationship between sleep and epilepsy has intrigued physicians and researchers. In the late nineteenth century, Gowers [1] commented on the relationship of seizures to the sleep-wake cycle. In 1929, Langdon-Down and Brain [2] observed that nocturnal seizures peaked approximately 2 hours after bedtime and between 4 AM and 5 AM, whereas daytime seizures were most prevalent in the first hour after waking. Berger's discovery of the electroencephalogram (EEG) in the 1920s provided a diagnostic tool for studies researching the interrelationship of sleep and epilepsy [3]. Gibbs and Gibbs [4] demonstrated that interictal epileptiform discharges were activated by sleep, and obtaining sleep during an EEG recording remains a standard activating procedure today. Janz [5] differentiated awakening, nocturnal, and diurnal/nocturnal epilepsies, and Niedermeyer [6] described the activating influence of arousal on epilepsy.

This review summarizes the basic mechanisms of epilepsy and the influence of sleep on epileptic seizures, highlights several epileptic syndromes that occur commonly during sleep, outlines the differential diagnosis of paroxysmal events and diagnostic tests for epilepsy, summarizes the evidence for sleep disorders in patients who have epilepsy, and discusses the management of sleep-related epilepsy.

Mechanisms

Epilepsy is a chronic disorder characterized by recurrent seizures. During seizures, abnormal electrical discharges are synchronized throughout a localized or distributed population of neurons in the brain [7]. Seizures may be partial, originating in a focal area of cortex, or generalized, arising diffusely from both hemispheres. Experimental models of partial and generalized epilepsy can be produced by applying chemicals, such as

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penicillin, directly to cortical tissue or by electrical stimulation. In the generalized epilepsies, spike and wave discharges seen in the human surface EEG are generated by thalamocortic neurons, with excitatory action potentials alternating with periods of inhibition [8], although cortical mechanisms also seem to be involved [9]. In experimental models of the partial epilepsies, the cellular correlate of the interictal spike is the paroxysmal depolarizing shift (PDS), a prolonged high-amplitude depolarization followed by a hyperpolarization [7]. A large excitatory postsynaptic potential underlies the PDS. A variety of mechanisms (including membrane receptor alterations and neurochemical release) operating at local (eg, hippocampal) and more widespread (eg, thalamocortic) levels are implicated in amplifying excitatory postsynaptic potential enhancement and PDS generation. The onset of seizure activity seems to be linked to attenuation of the hyperpolarizing membrane potential.

Sleep is an example of a physiologic state capable of modulating seizures through the involvement of widespread circuits, including thalamocortic networks [10]. The influence of sleep on epilepsy is supported by observation that, in specific epileptic syndromes, seizures occur exclusively or primarily during non–rapid eye movement (NREM) sleep. In almost all epileptic syndromes, interictal epileptiform discharges are more prevalent during NREM sleep and less prevalent during rapid eye movement (REM) sleep. Neuronal synchronization within thalamocortic networks during NREM sleep results in enhanced neuronal excitability, leading to more diffuse distribution of focal discharges and facilitation of seizures and interictal epileptiform discharges in many persons who have partial epilepsy. Neuronal synchronization is disrupted on arousal or transition to REM sleep, and focal discharges become more localized [11]. The biochemical pharmacology of sleep and arousal is under intensive study; the involvement of a variety of neurotransmitters is likely. The preoptic area of the hypothalamus is a major sleep-promoting system that uses γ-aminobutyric acid (GABA) as a neurotransmitter. Sleep-active neurons in the preoptic area project to brainstem regions that contain neurons involved in arousal from sleep and, by inhibiting these regions, in turn promote sleep. These regions include the pedunculopontine and laterodorsal tegmental nuclei, the locus coeruleus, and the dorsal raphe [12].

Epileptic syndromes associated with sleep

The proportion of patients who have seizures that occur exclusively or predominantly during sleep ranges from 7.5% to 45% in several series studying sleep-related epilepsy [13,14]. This wide variation in prevalence may reflect differences in epileptic syndromes among patient populations, with seizures more likely to occur during sleep in certain epileptic syndromes. The 1989 Classification and Terminology of the International League Against Epilepsy [15], the most widely used classification of the epilepsies,

distinguishes a variety of epileptic syndromes primarily on the basis of clinical characteristics, epidemiology, and EEG and neuroimaging studies.

A major discriminating factor is whether or not seizures originate in a group of neurons within one hemisphere (partial, focal, or localization related) or within neurons throughout both hemispheres (generalized). Specific partial and generalized epileptic syndromes associated with sleep are described in this article and outlined in Table 1. Two probable epileptic syndromes—paroxysmal nocturnal dystonia and epileptic arousals from sleep—also are discussed.

Partial seizures

Crespel and colleagues [16] found that frontal lobe seizures are more common during sleep and temporal lobe seizures more common during wakefulness. Herman and coworkers analyzed 613 seizures in 133 patients who had partial seizure and underwent video-EEG monitoring [17]. Forty-three percent of all partial seizures began during sleep, the majority during stages 1 and 2 sleep and none during REM sleep. Temporal lobe seizures were more likely to generalize secondarily during sleep than wakefulness compared with frontal lobe seizures, which were less likely to generalize secondarily during sleep. Frontal lobe seizures were most likely to occur during sleep, with temporal lobe seizures next, and occipital or parietal lobe seizures occurring rarely during sleep. Minecan and coworkers [18] show that seizures statistically were more common during NREM stages 1 and 2, at least for isolated seizures occurring in one night. Some seizures did occur during REM sleep, but this was the least frequent sleep stage for seizures to occur. Log delta power, an automated measure of sleep depth, increased in the 10 minutes before seizures, suggesting that seizures occur as sleep is deepening within NREM stages 1 and 2 sleep.

Temporal lobe epilepsy

Complex partial seizures that begin focally and impair consciousness are the predominant seizure type in temporal lobe epilepsy (TLE) [19]. Staring,

Table 1
Epilepsy syndromes associated with sleep-related seizures

Epilepsy syndrome	Age of onset
TLE	Late childhood to early adulthood
Frontal lobe epilepsy	Late childhood to early adulthood
Benign childhood epilepsy with centrotemporal spikes	3–13 y (peak 9–10 y)
Epilepsy with GTCS on awakening	6–25 y (peak 11–15 y)
Juvenile myoclonic epilepsy	12–18 y (peak 14 y)
Absence epilepsy	3–12 y (peak 6–7 y)
Lennox-Gastaut syndrome	1–8 y (peak 3–5 y)
Continuous spike and slow wave discharges during sleep	8 mo–11.5 y

orofacial or limb automatisms, and head and body movements occur frequently. The most common cause is idiopathic; trauma, tumor, stroke, and other focal lesions must be considered and are detectable with brain MRI. Idiopathic cases often show hippocampal sclerosis on MRI. Most patients continue to have seizures and require antiepileptic drug therapy; many patients, however, are controlled easily.

Because TLE is the most common type of partial epilepsy in adults, seizures during sleep commonly are of temporal lobe origin. In most patients who have TLE, however, seizures are more likely to occur during wakefulness than sleep. Bernasconi and colleagues [20] identified a group of 26 patient who had nonlesional refractory TLE and in whom seizures occurred exclusively or predominantly (> 90%) after they fell asleep or before they awakened. These patients manifested the typical clinical manifestations of TLE, and in addition, some also exhibited sleepwalking as a manifestation of their seizure activity. Their prognosis for seizure freedom after epilepsy surgery was more favorable than in patients who had nonlesional TLE and seizures during wakefulness.

Although temporal lobe seizures occur more frequently during NREM than REM sleep [17], they may occur occasionally during REM sleep [18]. Interictal epileptiform activity is more common during NREM sleep than during wakefulness and REM sleep. Sammaritano and colleagues [21] found that 78% of subjects had increases in the frequency of spikes recorded by surface electrodes during NREM stages 3 and 4 and that the field of spiking increased in NREM sleep compared with wakefulness and REM sleep. Increased spiking during deep NREM sleep also was found in depth electrode studies [22,23]. Overnight sleep recordings may reveal interictal foci not present on routine EEGs, thus providing prognostic information for the epilepsy surgery evaluation, especially in cases where the interictal spiking remains unilateral [24]. Examples of interictal epileptiform activity are shown in Figs. 1 and 2.

Frontal lobe epilepsy

As with temporal lobe epilepsy, the most common cause of frontal lobe epilepsy is idiopathic, although focal lesions also may be the cause. As the clinical manifestations of nocturnal frontal lobe seizures often include prominent tonic or motor manifestations, they are more likely to be noticed by the patient or family than complex partial seizures of temporal lobe origin; however, the brevity, the minimal amount or lack of postictal confusion, the psychogenic-appearing features (including kicking, thrashing, and vocalizations), and the frequently normal interictal and ictal recordings may complicate diagnosis. Nocturnal episodes may suggest diagnoses of sleep terrors, REM sleep behavior disorder (RBD), psychogenic spells, or paroxysmal nocturnal dystonia (discussed later). Scheffer and colleagues [25] describe an autosomal dominant nocturnal frontal epilepsy syndrome

Fig. 1. Right anterior temporal interictal epileptiform discharge with phase reversal at F8 electrode during stage 2 NREM sleep. Calibration symbol: 150 µV, 1 s.

(ADNFLE) with clustering of nocturnal motor seizures documented by video-EEG monitoring. Many of the 39 individuals from six families had been misdiagnosed with nonepileptic disorders. This large Australian kindred showed a missense mutation in the alpha-4 subunit of the neuronal
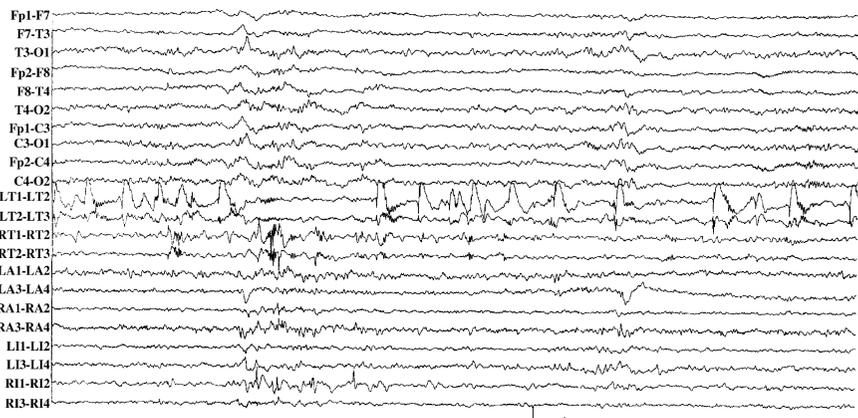

Fig. 2. Bilateral independent interictal epileptiform discharges from temporal depth electrode contacts RT1–RT2, RT2–RT3 (right anterior hippocampus) and LT1–LT2, LT2–LT3 (left anterior hippocampus). Note absence of interical epileptiform activity on simultaneously recorded scalp electrodes. Calibration symbols: 30 µV, 1 s (surface electrodes); 150 µV, 1 s (intracranial electrodes).

nicotinic acetylcholine receptor gene, located on chromosome 20q. This aberrant acetylcholine receptor may be related to the preferential occurrence of ADNFLE during sleep, in that physiologic sleep mechanisms are disrupted [26]. This model is complicated; independent investigators have determined that ADNFLE is a genetically heterogeneous disorder, however, with other families not showing linkage to chromosome 20q [27].

Frontal lobe seizures arise from a variety of structures, including the supplementary motor area; the cingulate gyrus; the anterior frontopolar, orbitofrontal, dorsolateral, and opercular regions; and the motor cortex. Correlation between anatomic location and clinical characteristics has limitations because of rapid propagation, although an anatomic classification still is used because of its simplicity. One example of frontal lobe epilepsy is the syndrome associated with supplementary sensorimotor area seizures that originate in or spread to involve area 6 on the medial surface of the cerebral hemisphere [28]. These seizures, which often occur in sleep, begin abruptly with tonic posturing of one or more extremities, sometimes followed by rhythmic or clonic movements. A sensation of pulling, pulsing, heaviness, numbness, or tingling may precede tonic posturing. The surface EEG often is normal, although interictal epileptiform activity or ictal patterns may occur in electrodes at or adjacent to the midline (ie, Cz). Seizures of sensorimotor area origin may be mistaken for psychogenic spells because of thrashing behavior, preservation of consciousness, absence of postictal confusion, and absence of interictal or ictal EEG activity. Diagnostic points supporting sensorimotor area seizures include (1) short duration (less than 30 seconds to a minute), (2) stereotyped nature, (3) tendency to occur predominantly or exclusively during sleep, and (4) tonic contraction of the arms in abduction. Psychogenic spells usually are longer in duration (1 to several minutes), are nonstereotypic, and occur in the awake or drowsy state [29]. Withdrawal of antiepileptic medications to promote generalized tonic-clonic seizures (GTCS) during in-patient evaluation with continuous video-EEG monitoring is a useful diagnostic maneuver [30].

Partial seizures with complex automatisms

Pedley and Guilleminault [31] describe six patients who had unusual sleepwalking episodes involving screaming or other vocalizations and complex, often violent automatisms. They distinguished these probable epileptic spells from NREM sleep confusional arousals (described previously) on the basis of several characteristics. Probable epileptic spells occurred in a slightly older age group (adolescents and young adults) in association with complex behaviors and complete unresponsiveness to the environment, with a family history for confusional arousals lacking. Epileptiform EEG abnormalities and responsiveness to antiepileptic medications also supported a diagnosis of epilepsy. Montagna and colleagues [32] performed EEG polysomnography in six patients who had

complex arousals from NREM sleep characterized by wandering, motor agitation, and screaming. One patient experienced GTCS after an EEG arousal, and two responded to carbamazepine, supporting a diagnosis of epilepsy.

Benign epilepsy of childhood with centrotemporal spikes

Also known as benign rolandic epilepsy, this common childhood seizure disorder, which accounts for 15% to 20% of childhood epilepsy, responds favorably to antiepileptic medication [33,34]. The cause is idiopathic, with a genetic predisposition. Seizures occur predominantly during sleep. Oropharyngeal signs, including hypersalivation and guttural sounds, are the most common manifestations. Speech arrest, clonic jerks, tonic contraction of the mouth, and occasionally clonic jerks of the arm or leg also are common. Consciousness is preserved in most cases unless secondary generalization occurs. The EEG usually shows centrotemporal or rolandic spikes or sharp waves, reflecting the anatomic areas underlying the most common clinical manifestations (Fig. 3).

Fig. 3. Runs of interictal epileptiform with a centrotemporal dominance in benign rolandic epilepsy. Calibration symbol: 500 µV, 1 s.

Generalized seizures

Epilepsy with generalized tonic-clonic seizures on awakening

In this idiopathic syndrome, which most likely has a genetic basis, GTCS occur exclusively or predominantly (>90%) shortly after awakening (regardless of time of day) or in the evening period of relaxation [13]. Myoclonic or absence seizures may coexist. Photosensitivity is common, and sleep deprivation is a frequent precipitant. The EEG shows interictal generalized spike-wave activity. Complete seizure control with medication occurs in most patients, although most relapse if medication is withdrawn.

Juvenile myoclonic epilepsy is a related syndrome. It is one of the most common forms of idiopathic generalized epilepsy, and consists of a combination of myoclonic seizures that occur shortly after awakening, GTCS, and absence seizures [35]. When questioned, patients may report being clumsy and dropping items while carrying out their morning activities of daily living, including shaving, applying cosmetics, or preparing breakfast. Brain MRI and neurologic examination are normal. Interictal EEGs in untreated patients are characterized by diffuse polyspike and slow wave complexes of 4 to 6 Hz. Response to antiepileptic medications usually is excellent, although lifelong treatment often is necessary.

Absence epilepsy

Absence epilepsy is another genetically determined form of generalized epilepsy. Seizures are brief spells, usually lasting less than 10 seconds, characterized by the abrupt cessation of ongoing activity, a blank stare, and abrupt return to awareness with resumption of activity [36]. Mild clonic, atonic, or tonic components or automatisms may be associated. They often are precipitated by hyperventilation, photic stimulation, and drowsiness and are suppressed by attention. The brevity of the attacks and the lack of an aura or postictal confusion help to distinguish these spells from complex partial seizures [37]. The waking EEG correlate to absence seizures is the classical 3-second spike and wave discharge. Drowsiness and sleep activate spike and wave discharges, which are most marked during the first sleep cycle, maximal during NREM sleep, and rare or absent in REM sleep [38]. The morphology of spike and wave discharges also is affected by NREM sleep, with irregular polyspike-wave discharges predominating. Prognosis with treatment is excellent. The seizures decrease with advancing age, and medications can be withdrawn from most patients by late adolescence, although some patients continue to require treatment for life.

Lennox-Gastaut syndrome

This syndrome is characterized by generalized tonic, atonic, and atypical absence seizures, slow background on interictal EEG with slow (usually 2.0–2.5 Hz) spike and wave complexes, and mental retardation [39]. There are cryptogenic forms with no prior neurologic abnormality, normal

development, and normal neuroimaging and symptomatic forms of other neurologic abnormalities, abnormal development, or abnormal neuro-imaging. NREM sleep is associated with increased spikes and rhythmic 10-Hz spikes that may be accompanied by tonic seizures.

Other epilepsies

In some epilepsy syndromes, it is uncertain if seizures are focal or generalized. Epilepsy with continuous spike-waves during slow wave sleep (CSWS) is one such syndrome, Patry and colleagues [40] described "subclinical" electrical status epilepticus induced by sleep in children with almost continuous spike and slow wave discharges during NREM sleep. The disorder affects only 0.5% of children with epilepsy, and its cause is unclear, although approximately one-third of children have neurologic abnormalities [41]. It is a striking form of epilepsy because of the markedly abnormal state dependent EEG: 2.0- to 2.5-Hz generalized spike and wave discharges occur during at least 85% of NREM sleep, whereas during REM sleep and wakefulness, spike-wave discharges are less continuous and more focal. Seizures are not universal, although they frequently occur in CSWS and may be manifested as nocturnal partial motor seizures or GTCS, atypical absence, or myoclonic jerks. Progressive behavioral disturbances are common. Although treatment of seizures is partially or completely effective, cognitive impairment usually persists.

Probable epileptic disorders

Nocturnal paroxysmal dystonia

This syndrome, initially termed hypnogenic paroxysmal dystonia and subsequently, nocturnal paroxysmal dystonia (NPD), is characterized by brief (15–45 seconds) stereotyped motor attacks consisting of dystonic posturing, ballistic or choreic dyskinesias, and vocalizations during NREM sleep without clear ictal or interictal EEG changes that are responsive to carbamazepine [42]. Although the lack of EEG changes might seem to make epilepsy an unlikely cause, the lack of surface EEG abnormalities does not exclude epilepsy; seizures originating in deep mesial frontal generators often lack interictal and ictal correlates and require invasive monitoring for definitive diagnosis. Tinuper and colleagues [43] report two patients who had "typical" NPD attacks that culminated in GTCS with electrographic ictal correlates. The attacks of NPD resemble frontal lobe seizures in their brevity and motor involvement. In evaluating a patient who has a history consistent with NPD, EEGs during wake and sleep should be performed. Additional supraorbital electrodes should be placed to increase frontal lobe coverage. Care should be taken to identify and differentiate central spikes from physiologic vertex sharp waves of sleep. Intracranial monitoring may be required for refractory cases in which there is a high suspicion of epilepsy.
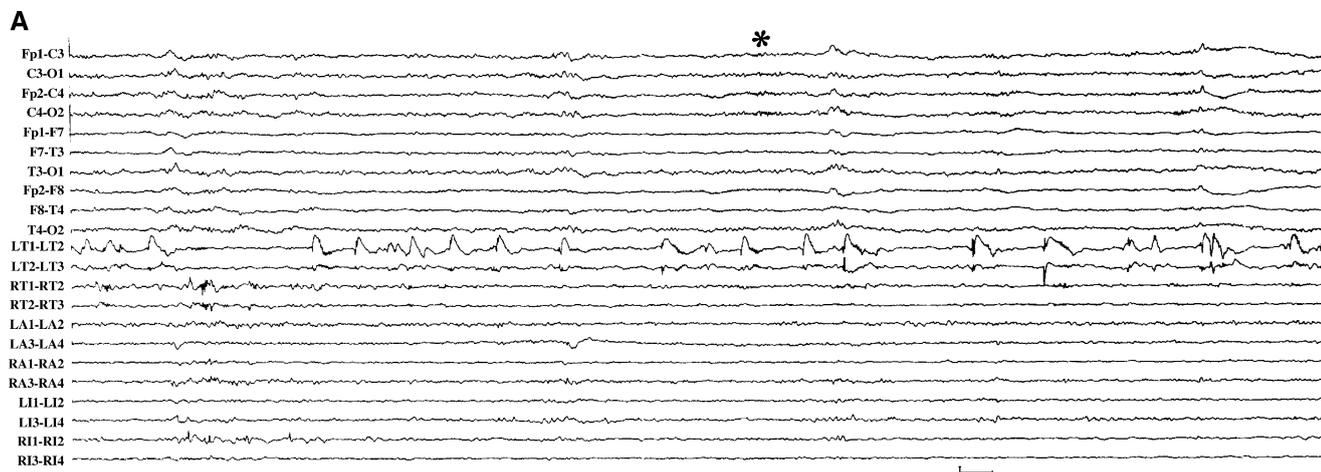
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Fig. 4. Combined surface electrode (first 10 channels) and intracranial montage (last 12 channels). Calibration symbols: 30 µV, 1 s (surface electrodes); 150 µV, 1 s (intracranial channels). (*A*) Prior to seizure onset, sleep spindles (*asterisk*) are apparent in the surface electrodes, and frequent interictal epileptiform discharges are observed in the left and right temporal depth electrode contacts (RT1–RT2, RT2–RT2 and LT1–LT2, LT2–LT3). (*B*) At the open arrow, the earliest definite intracranial ictal discharge (spike and wave complex in the right temporal depth electrode contacts leading to rhythmic sinusoidal alpha frequency activity) is seen, preceding the clinical arousal from sleep (*solid arrow*, indicating myogenic activity) and the earliest definite scalp ictal discharge (*bracket*, indicating myogenic activity with emerging right temporal rhythmic theta activity). (*From* Malow BA, Varma NK. Seizures and arousals from sleep—which comes first? Sleep 1995;18:783–6; with permission.)
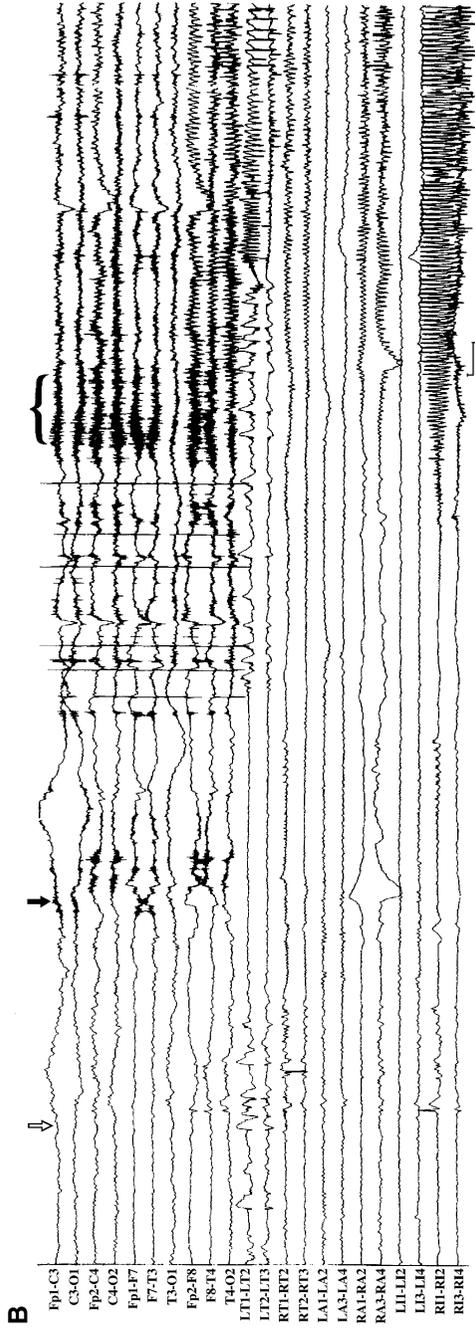
Fig. 4 (*continued*)

"Epileptic" arousals from sleep

Athough most arousals from sleep are not the result of epilepsy, epileptic seizures and interictal epileptiform activity sometimes may be associated with arousals and excessive daytime somnolence. In two of the epilepsy syndromes described previously—epilepsy with GTCS on awakening and juvenile myoclonic epilepsy—transition from the sleep to wake state is a clear precipitant. Peled and Lavie [44] describe 14 patients who had hypersomnolence and paroxysmal epileptic discharges during stages 2 and 3 of NREM sleep that were associated with arousals, fragmentation of sleep, and reduction in sleep efficiency, in particular REM sleep. Three of these patients responded to anticonvulsant agents with a clinical and polysomnographic improvement in sleep patterns.

It is important to recognize the shortcomings of surface EEG when investigating the relationship between arousals and seizures. In cases in which seizures seem to follow clinical arousals, the onset of ictal activity may be delayed on the surface EEG compared with the intracranial EEG [45]. Fig. 4 illustrates an example from combined surface intracranial monitoring in which the surface EEG does not demonstrate ictal activity until several seconds after a clinical arousal from sleep. The concomitant intracranial EEG reveals seizure onset just before the clinical arousal from sleep.

Differential diagnosis

The differentiation of nocturnal seizures from nonepileptic spells during sleep can be challenging for several reasons (Box 1). First, in partial seizures occurring during wakefulness, patients may report postictal confusion or recall the beginning of a seizure (aura) that precedes loss of consciousness. These elements of the history support the diagnosis of epilepsy and frequently are absent in seizures occurring during sleep. Second, nocturnal events may not be observed properly. Bed partners may not be present or, if present, may not be fully awake and coherent. Complex partial seizures of temporal lobe origin in particular may lack vigorous motor activity and may fail to wake the bed partner. Third, a variety of sleep disorders (discussed later) are characterized by vigorous movements and behaviors that mimic seizures. Finally, certain types of seizures, particularly those of frontal lobe origin, are manifested by bizarre movements suggestive of a psychiatric disorder, including kicking, thrashing, and vocalizations. These epilepsies may be associated with normal ictal and interictal EEGs and normal imaging studies, making definitive diagnosis difficult.

Non–rapid eye movement arousal disorders

NREM arousal disorders include a spectrum of confusional arousals, somnambulism (sleepwalking), and night terrors. These three disorders share

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Box 1. Differential diagnosis of nocturnal spells

Epileptic seizures
Frontal lobe epilepsy
TLE
GTCS
Benign rolandic epilepsy

Probable epileptic seizures
NPD
Epileptic arousals from sleep

NREM arousal disorders
Confusional arousals
Night terrors
Somnambulism

REM sleep behavior disorder
Sleep-related movement disorder
PLMS
Sleep-onset myoclonus
Bruxism
Rhythmic movement disorder

Psychiatric disorders
Nocturnal panic disorder
Post-traumatic stress disorder
Psychogenic seizures

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the following features: (1) they usually arise from NREM stages 3 or 4 sleep and, therefore, occur preferentially in the first third of the sleep cycle when NREM stages 3 and 4 are predominant; (2) they are more common in childhood; and (3) a positive family history frequently is elicited, suggesting a genetic component. Broughton [46] contrasted confusional arousals, characterized by body movement, autonomic activation, mental confusion and disorientation, and fragmentary recall of dreams with the nightmares of REM sleep, in which subjects became lucid almost immediately and usually recalled dreaming. Somnambulism is a related NREM arousal disorder in which patients may wander out of the bedroom or house during confusional episodes. Night terrors begin with an intense scream followed by vigorous motor activity. Children often are inconsolable and completely amnestic for the event. The subject appears to be awake but is unable to perceive the environment. If mental activity preceding the event is recalled, the images are simple (eg, face, animal, or fire) compared with the complex plots of REM nightmares. Patients often report an oppressive experience, such as being locked up in a tomb, or having rocks piled on their chests. Intense autonomic

activation results in diaphoresis, mydriasis, tachycardia, hypertension, and tachypnea [47]. In contrast to seizures, NREM arousal disorders are less stereotyped and commonly occur in the first third of the night.

Rapid eye movement sleep behavior disorder

Patients who have this disorder often present with vigorous motor activity during sleep [48]. Patients may injure themselves or their bed partners. In RBD, the physiologic muscle atonia present during REM sleep is absent; persistence of muscle tone enables patients to act out their dreams. Episodes of RBD are less stereotyped, longer in duration, and more likely to begin after age 50 compared with epileptic seizures. Apart from seizures, the other major consideration in patients presenting with vigorous motor activity is obstructive sleep apnea with resulting arousals from sleep. Diagnosis is confirmed by video-EEG polysomnography (VPSG), demonstrating either a behavioral episode consistent with RBD or the persistence of muscle tone during REM sleep.

Sleep-related movement disorders

Movement disorders occurring during sleep that may resemble seizures include periodic limb movements, sleep-onset myoclonus, bruxism, and rhythmic movement disorder. Periodic limb movements in sleep (PLMS) may result in vigorous kicking or thrashing. A history of restless legs syndrome commonly is elicited [49]. In contrast to seizures, PLMS occur at periodic intervals (usually every 20 to 40 seconds) and involve a characteristic flexion of the leg, although the upper extremities occasionally may be involved. Sleep-onset myoclonus, also known as sleep starts, sleep jerks, or hypnic jerks, is a normal physiologic event occurring at the transition from wakefulness to sleep, often associated with sensory phenomena, including a sensation of falling. In contrast to myoclonic seizures, sleep-onset myoclonus is limited to sleep onset. Bruxism, manifested as stereotyped teeth grinding resembling rhythmic jaw movements of epilepsy, may lead to excessive tooth wear, which does not occur in epilepsy [50]. Rhythmic movement disorder, also known as head banging or body rocking, can occur during any sleep stage [51]. It is manifested in a variety of ways, including recurrent banging of the head while the patient is prone or rocking of the body back and forth while on hands and knees. Vocalizations may accompany the repetitive movements. Rhythmic movement disorder can occur at any age, although it is more common in children than adults and is associated with mental retardation. Although complex partial seizures, particularly those of frontal lobe origin, may include similar behaviors, bilateral body rocking is more characteristic of rhythmic movement disorder. Body rocking also may occur in psychogenic seizures.

Psychiatric disorders

Psychiatric disorders occurring during sleep that resemble seizures include panic attacks during sleep, post-traumatic stress disorder, and psychogenic seizures. Some patients who have panic disorder present exclusively or predominantly with panic episodes that cause multiple abrupt awakenings from sleep. Symptoms on awakening include apprehension and autonomic arousal, with palpitations, dizziness, and trembling [52]. In contrast to nightmare of REM sleep, dreams are not recalled. In contrast to night terrors, which arise out of deep NREM sleep, sleep panic usually occurs in the transition from NREM stages 2 to 3 [53]. Although a history of daytime panic attacks can be useful diagnostically, panic attacks may occur exclusively during sleep. An abrupt return to consciousness and autonomic arousal is more characteristic of panic disorder than seizures, although these features may occur in seizures. Simple partial seizures of parietal lobe origin may manifest occasionally as panic symptoms [54].

Post-traumatic stress disorder occurs after major psychologic trauma, such as combat situations and physical abuse. Repetitive rocking or head banging may occur, and the characteristic nightmares or flashbacks may arise from any stage of sleep [55]. In contrast to seizures, patients often experience the recall of true traumatic experiences.

Psychogenic seizures may occur during apparent sleep [56]. The diagnosis of these nonepileptic events is supported by the presence of a well-organized posterior alpha rhythm immediately before the onset of clinical changes despite the appearance of sleep and the lack of ictal or postictal EEG changes. Provocative testing with suggestion may be helpful in confirming the diagnosis of psychogenic seizures.

Video-electroencephalogram polysomnography

VPSG combines video-EEG monitoring with standard polysomnographic recordings and can be helpful in distinguishing epilepsy from other sleep disorders (Fig. 5) [57]. The video component is essential in characterizing spells; a stereotyped behavioral pattern, such as consistent head turning to one side, or a consistent automatism is highly suggestive of epilepsy. The stage of sleep from which the spells emerge can be useful in supporting the diagnosis of confusional arousals or RBD. Seizures, however, may emerge from any stage of sleep and may coexist with sleep disorders. The extensive EEG coverage provided by VPSG may detect interictal epileptiform activity or seizures; nonetheless, EEG studies may be completely normal in epilepsy. Finally, the coexisting standard PSG monitoring may detect coexisting sleep disorders, such as obstructive sleep apnea, which may exacerbate an underlying seizure disorder (discussed later) or mimic RBD.

An important limitation of VPSG is that the patient's habitual events, even if nightly, may not occur in the sleep laboratory; a similar phenomenon is observed in epilepsy monitoring units and may be related to the
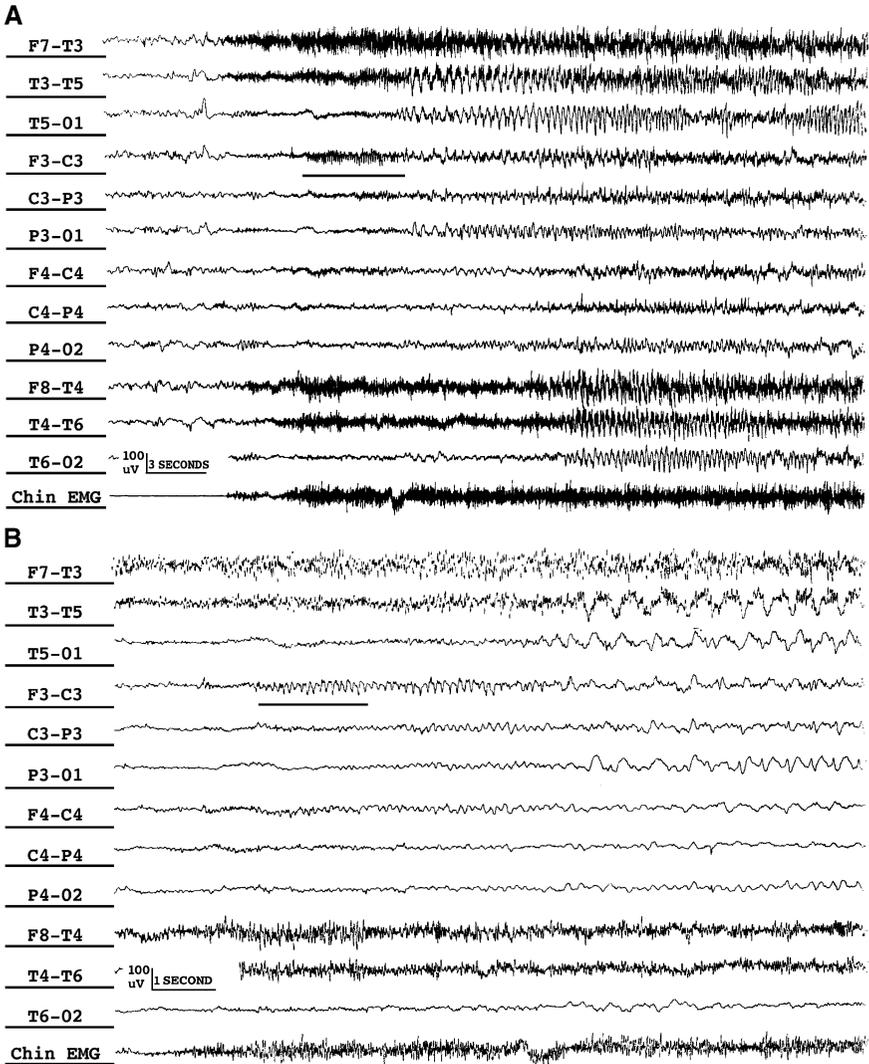
Fig. 5. EEG polysomnogram showing the onset of a partial seizure recorded at 10 mm/s paper speed. Clinically, the seizure began with an abrupt arousal, followed by turning of head and eyes to the left and movements of the arms beneath the bedclothes. On EEG, there is an initial electrodecremental event followed by a progressive increase in the amplitude of the ictal discharge over the left hemisphere and a spread to the right hemisphere derivations. The underlined activity (*A*) from the F3–C3 derivation seems to be muscle artifact; however, in (*B*), at 30 mm/s paper speed, the same underlined segment is the initial focal surface representation of the ictal discharge. Additional polysomnographic measurements recorded on channels 14 to 21 are not shown. (*From* Aldrich MS, Jahnke BA. Diagnostic value of video-EEG polysomnography. Neurology 1991;41:1060–6; with permission.)

unfamiliar surrounding or a change in the usual routine. Sleep deprivation may be useful in provoking events consistent with NREM arousal disorders. In patients who have suspected RBD, it is not necessary to capture a behavioral event; the persistence of chin EMG with increased phasic activity during REM sleep in the setting of compelling history is sufficient. In patients who have suspected epileptic seizures, subclinical ictal and interictal seizures in the absence of behavioral events support the diagnosis of epilepsy but are not diagnostic.

Sleep disorders and epilepsy

Sleep disorders are common, treatable conditions that frequently coexist with epilepsy. Epilepsy and its treatment, including antiepileptic drugs, may affect sleep organization and contribute to daytime sleepiness, insomnia, or sleep disorders, such as obstructive sleep apnea. Conversely, treatment of a coexisting sleep disorder may improve seizure control, daytime alertness, or both. Sleep disorders are covered in detail in articles elsewhere in this issue; the focus of this discussion is on the overlap of sleep disorders with epilepsy.

Antiepileptic medications may influence sleep. The barbiturates and benzodiazepines, which are sedating and suppress REM sleep [58], should be avoided if possible. In two independent studies of lamotrigine in patients who have epilepsy, this medication enhanced REM sleep [59] or did not suppress REM sleep [60]. Therefore, lamotrigine may be a useful antiepileptic drug in patients who have suppressed REM sleep at baseline. Gabapentin increases slow wave sleep in healthy adults [61] and may be useful in patients who have epilepsy and suppressed slow wave sleep at baseline. A provocative question is whether or not part of the beneficial effect of antiepileptic drugs on seizure control is related to consolidation of sleep.

Vagus nerve stimulation, a novel treatment option for refractory partial seizures, improved daytime sleepiness in 16 patients who had epilepsy [62]. This improvement may result from vagal afferents projecting to brainstem regions that promote alertness, such as the parabrachial nucleus. Alternatively, vagus nerve stimulation produces decreases in respiratory airflow and effort during sleep, and may exacerbate obstructive sleep apnea [63,64]. The etiology of these sleep-related respiratory effects might be either peripheral (vagal efferents to upper airway musculature) or central (vagal input to brainstem nuclei that regulates breathing).

Symptoms of drowsiness in a patient on antiepileptic drugs that do not seem dose-dependent or related to frequent seizures may be the result of a sleep disorder. In a study of predictors of sleepiness in patients who have epilepsy, symptoms of obstructive sleep apnea or restless legs syndrome were

more significant predictors of elevated scores on the Epworth Sleepiness Scale than the number or type of antiepileptic medication, seizure frequency, epilepsy syndrome, or the presence of sleep-related seizures [65]. In a separate study, patients who had refractory epilepsy had a high prevalence of obstructive sleep apnea, one third with an apnea-hypopnea index of 5 or more episodes an hour on polysomnography. Increased age, male gender, and seizures during sleep were associated with obstructive sleep apnea [66]. Of note, treatment of obstructive sleep apnea in case series [67–69] and open-label trials [70] has led to improvements in seizure frequency and daytime sleepiness. The mechanism underlying the improvement in seizure frequency is not clear and may be related to amelioration of sleep deprivation or consolidation of sleep with reductions in sleep stage shifts, which tend to facilitate seizures [18].

Management considerations in patients who have sleep-related seizures

The treatment of nonepileptic sleep disorders mimicking epilepsy is described in this article and in detail elsewhere in this issue. The reader is referred to a standard textbook on epilepsy for treatment of epileptic seizures, including medications, epilepsy surgery, and other modalities [71]. In patients who have sleep-related seizures, it often is helpful for the largest dose to be taken before bedtime to maximize seizure control. Avoidance of sleep deprivation is recommended. Somnolence is a common adverse effect of antiepileptic medications; small initial doses of medication with gradual increases as needed minimize but do not eliminate somnolence.

In patients who have rare seizures limited to sleep, the decision to initiate medication therapy should be individualized. Some patients prefer to have an occasional seizure and avoid the side effects of daily antiepileptic medication. Patients who have seizures during sleep should be counseled about state driving restrictions; some licensing authorities may permit those who have seizures occurring only during sleep to drive, although requirements vary greatly among states [72].

The prognosis of seizures is influenced by the epilepsy syndrome and the underlying cause. For example, benign epilepsy of childhood with centrotemporal spikes has an excellent prognosis, and antiepileptic drugs can be discontinued in most cases by late adolescence. Patients who have complex partial seizures of temporal or frontal lobe origin have an intermediate and variable prognosis. Lennox-Gastaut syndrome is poorly responsive to medications in most cases.

Summary

This article examines the relationship between sleep and epilepsy, an association that has been recognized since antiquity. The mechanisms whereby sleep facilitates seizures are under investigation, although the

synchronizing role of thalamocortic networks seems contributory. Recognition of the variety of generalized and partial epileptic syndromes associated with sleep, familiarity with the differential diagnosis of nocturnal spells, and awareness of the role that antiepileptic drugs and sleep disorders may play in epilepsy are helpful in evaluating patients presenting with behavioral and motor disturbances of sleep.

References

[1] Gowers WR. Epilepsy and other chronic convulsive diseases, vol. 1. London: Williams Wood; 1885.

[2] Langdon-Down M, Brain WR. Time of day in relation to convulsions in epilepsy. Lancet 1929;2:1029.

[3] Goldensohn ES. Historical perspectives and future directions. In: Wyllie E, editor. The treatment of epilepsy: principles and practice. Philadelphia: Lea & Febiger; 1993. p. 173.

[4] Gibbs E, Gibbs FA. Diagnostic and localizing value of electroencephalographic studies in sleep. Res Publ Assoc Res Nerv Ment Dis 1947;26:366.

[5] Janz D. The grand mal epilepsies and the sleeping-waking cycle. Epilepsia 1962;3:69.

[6] Niedermeyer E. Generalized seizure discharges and possible precipitating mechanisms. Epilepsia 1966;7:23.

[7] Lothman EW, Bertram EH III, Stringer JL. Functional anatomy of hippocampal seizures. Prog Neurobiol 1991;32:1.

[8] Gloor P, Fariello RG. Generalized epilepsy: some of its cellular mechanisms differ from those of focal epilepsy. Trends Neurosci 1988;11:63.

[9] Timofeev I, Bazhenov M, Sejnowski T, et al. Cortical hyperpolarization-activated depolarizing current takes part in the generation of focal paroxysmal activities. Proc Natl Acad Sci USA 2002;99:9533.

[10] Steriade M, McCormick DA, Sejnowski TJ. Thalamocortical oscillations in the sleeping and aroused brain. Science 1993;262:679.

[11] Steriade M, Contreras D, Amzica F. Synchronized sleep oscillations and their paroxysmal developments. Trends Neurosci 1994;17:199.

[12] Saper CB, Chou T, Scammell TE. The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci 2001;24:726.

[13] Janz D, Wolf P. Epilepsy with grand mal on awakening. In: Engel J Jr, Pedley T, editors. Epilepsy: a comprehensive textbook. Philadephia: Lippincott Raven; 1998. p. 2347.

[14] Young GB, Blume WT, Wells GA, et al. Differential aspects of sleep epilepsy. Can J Neurol Sci 1985;12:317.

[15] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389.

[16] Crespel A, Baldy-Moulinier M, et al. The relationship between sleep and epilepsy in frontal and temporal lobe epilepsies: practical and physiopathologic considerations. Epilepsia 1998; 39:150.

[17] Herman ST, Walczak TS, Bazil CW. Distribution of partial seizures during the sleep wake cycle. Differences by seizure onset site. Neurology 2001;56:1453.

[18] Minecan DA, Natarajan A, Marzec M. Relationship of epileptic seizures to sleep stage and sleep depth. Sleep 2002;25:899.

[19] Williamson PD, Engel J Jr. Complex partial seizures. In: Engel J Jr, Pedley TA, editors. Epilepsy: a comprehensive textbook. Philadelphia: Lippincott-Raven Publishers; 1997. p. 557.

[20] Bernasconi A, Andermann F, et al. Nocturnal temporal lobe epilepsy. Neurology 1998;50: 1772.

[21] Sammaritano M, Gigli GL, Gotman J. Interictal spiking during wakefulness and sleep and localization of foci in temporal lobe epilepsy. Neurology 1991;41:290.

[22] Lieb J, Joseph JP, Engel J Jr, et al. Sleep state and seizure foci related to depth spike activity in patients with temporal lobe epilepsy. Electroencephalogr Clin Neurophysiol 1980;49:538.

[23] Rossi GF, Colicchio G, Pola P. Interictal epileptic activity during sleep: a stereo-EEG study in patients with partial epilepsy. Electroencephalogr Clin Neurophysiol 1984;58(2):97–106.

[24] Malow BA, Selwa LM, Ross D, et al. Lateralizing value of interictal spikes on overnight sleep-EEG studies in temporal lobe epilepsy. Epilepsia 1999;40:1587.

[25] Scheffer IE, Bhatia KP, Lopes-Cendes I. Autosomal dominant frontal epilepsy misdiagnosed as sleep disorder. Lancet 1994;343:515.

[26] di Corcia G, Blasetti A, De Simone M, et al. Recent advances in autosomal dominant nocturnal frontal lobe epilepsy: 'understanding the nicotinic acetylcholine receptor (nAChR)'. Eur J Paediatr Neurol 2005;9:59.

[27] Oldani A, Zucooni M, Asselta R, et al. Autosomal dominant nocturnal frontal lobe epilepsy. A video-polysomnographic and genetic appraisal of 40 patients and delineation of the epileptic syndrome. Brain 1998;121:205.

[28] Kellinghaus C, Lüders HO. Frontal lobe epilepsy. Epileptic Disord 2004;6:223.

[29] Kanner AM, Morris HH, Lüders H, et al. Supplementary motor seizures mimicking pseudoseizures: some clinical differences. Neurology 1990;40:1404.

[30] Goldstick L, Lesser RP, Lüders H, et al. The need for anticonvulsant drug withdrawal in the diagnosis of supplementary motor seizures. Epilepsia 1985;26:231.

[31] Pedley TA, Guilleminault C. Episodic nocturnal wanderings responsive to anticonvulsant drug therapy. Ann Neurol 1977;2:30.

[32] Montagna P, Sforza E, Tinuper P, et al. Paroxysmal arousals during sleep. Neurology 1990; 40:1063.

[33] Louseau P, Duche B. Benign childhood epilepsy with centrotemporal spikes. Clev Clin J Med 1989;56:17.

[34] Wirrel E. Benign epilepsy of childhood with centrotemporal spikes. Epilepsia 1998;39:S32.

[35] Grunewald R, Panayiotopoulos C. Juvenile myoclonic epilepsy: a review. Arch Neurol 1993; 50:594.

[36] Gomez MR, Westmoreland BF. Absence seizures. In: Lüders H, Lesser RP, editors. Epilepsy: electroclinical syndromes. New York: Springer-Verlag; 1987. p. 105.

[37] Theodore WH, Porter RJ, Penry JK. Complex partial seizures: clinical characteristics and differential diagnosis. Neurology 1983;33:1115.

[38] Sato S, Dreifuss F, Penry JK. The effect of sleep on spike-wave discharges in absence seizures. Neurology 1973;2:1335.

[39] Markand ON. Lennox-Gastaut syndrome (childhood epileptic encephalopathy). J Clin Neurophysiol 2003;20:426.

[40] Patry G, Lyagoub S, Tassinari CA. Subclinical electrical status epilepticus induced sleep in children. Arch Neurol 1971;24:242.

[41] Tassinari CA, Rubboli G, Volpi L. Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the aquired aphasia. Clin Neurophysiol 2000; 111(Suppl 2):S94.

[42] Lugaresi E, Cirignotta F, Montagna P. Nocturnal paroxysmal dystonia. Epilepsy Res Suppl 1991;2:137–40.

[43] Tinuper P, Cerullo A, Cirignotta F, et al. Nocturnal paroxysmal dystonia with short lasting attacks: three cases with evidence for an epileptic frontal lobe origin of seizures. Epilepsia 1990;31:549.

[44] Peled R, Lavie P. Paroxysmal awakenings from sleep associated with excessive daytime somnolence: a form of nocturnal epilepsy. Neurology 1986;36:95.

[45] Malow BA, Bowes R, Ross D. Relationship of temporal lobe seizures to sleep and arousal—a combined scalp-intracranial electrode study. Sleep 2000;23:231.

[46] Broughton RJ. Sleep disorders: disorders of arousal? Science 1968;159:1070.

[47] Mahowald MW, Ettinger MG. Things that go bump in the night: the parasomnias revisited. J Clin Neurophysiol 1990;7(1):119–43.

[48] Mahowald M, Schenck C. REM sleep parasomnias. In: Kryger M, Roth T, Dement W, editors. Principles and practice of sleep medicine. 4th edition. Philadelphia: Elsevier-Saunders; 2005. p. 897.

[49] Walters AS, Hening WA, Chokroverty S. Review and videotape recognition of idiopathic restless legs syndrome. Mov Disord 1991;6:105.

[50] Lavigne GJ, Manzini C, et al. Sleep bruxism. Principles and practice of sleep medicine. In: Kryger M, Roth T, Dement W, editors. Principles and practice of sleep medicine. 4th edition. Philadelphia: Elsevier-Saunders; 2005. p. 946.

[51] Hoban TF. Rhythmic movement disorder in children. CNS Spectr 2003;8:135.

[52] Mellman TA, Uhde TW. Patients with frequent sleep panic: clinical findings and response to medication treatment. J Clin Psychiatry 1990;51:513.

[53] Mellman TA, Uhde TW. Electroencephalographic sleep in panic disorder. Arch Gen Psychiatry 1989;46:178.

[54] Alemayehu S, Bergey GK, Barry E, et al. Panic attacks in ictal manifestations of parietal lobe seizures. Epilepsia 1995;36:824–30.

[55] Hefez A, Metz L, Lavie P. Long-term effects of extreme situational stress on sleep and dreaming. Am J Psychiatry 1987;144:344.

[56] Thacker K, Devinsky O, Perrine K, et al. Nonepileptic seizures during apparent sleep. Ann Neurol 1993;33:414.

[57] Aldrich MS, Jahnke B. Diagnostic value of video-EEG polysomnography. Neurology 1991; 41:1060.

[58] Placedi F, Marciani MG, Diomedi M, et al. Effects of lamotrigine on nocturnal sleep, daytime somnolence and cognitive functions in focal epilepsy. Acta Neurol Scand 2000;102:81.

[59] Placedi F, Scalise A, Marciani MG, et al. Effect of antiepileptic drugs on sleep. Clin Neurophys 2000;111(Suppl 2):S115.

[60] Foldvary N, Perry M, Lee J, et al. The effects of lamotrigine on sleep in patients with epilepsy. Epilepsia 2001;42:1569.

[61] Foldvary-Schaefer N, Sanchez ID, Karafa M, et al. Gabapentin increases slow-wave sleep in normal adults. Epilepsia 2002;43:1493.

[62] Malow BA, Edwards J, Marzec M, et al. Vagus nerve stimulation reduces daytime sleepiness in epilepsy patients. Neurology 2001;57:879.

[63] Malow BA, Edwards J, Marzec M, et al. Effects of vagus nerve stimulation on respiration during sleep: a pilot study. Neurology 2000;55:1450.

[64] Marzec M, Edwards J, Sagher O, et al. Effects of vagus nerve stimulation on sleep-related breathing in epilepsy patients. Epilepsia 2003;44:930.

[65] Malow BA, Bowes R, Lin X. Predictors of sleepiness in epilepsy patients. Sleep 1997;20:1105.

[66] Malow BA, Levy K, Maturen K, et al. Obstructive sleep apnea is common in medically refractory epilepsy patients. Neurology 2000;55:1002.

[67] Devinsky O, Ehrenberg B, Barthlen GM, et al. Epilepsy and sleep apnea syndrome. Neurology 1994;44:2060.

[68] Vaughn BV, Messenheimer JA, D'Cruz OF. Sleep apnea in patients with epilepsy. Epilepsia 1993;34:136.

[69] Malow BA, Fromes GA, Aldrich MS. Usefulness of polysomnography in epilepsy patients. Neurology 1997;48(5):1389–94.

[70] Malow BA, Weatherwax KJ, Chervin RD, et al. Identification and treatment of obstructive sleep apnea in adults and children with epilepsy: a prospective pilot study. Sleep Med 2003;4: 509.

[71] Engel J Jr, Pedley T, editors. Epilepsy: a comprehensive textbook. Philadephia: Lippincott Raven; 1998. p. 2347.

[72] Yale SH, Hansotia P, Knapp D, et al. Neurologic conditions: assessing medical fitness to drive. Clin Med Res 2003;1:177.