Review Article

Sleep and epilepsy in children and adolescents

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Abstract

Epilepsy and sleep disorders are considered by many to be common bedfellows. Several sleep phenomena may occur during nighttime taking a wide variety of forms and which can mimic seizures. Although most seizure sub-types have the potential to occur during sleep or wakefulness, sleep has a well-documented and strong association with specific epilepsy syndromes. Seizures in sleep also tend to occur during lighter stages of non-REM (NREM) sleep. The neurophysiologic process involved in the deepening of NREM sleep may also facilitate both seizures and IEDs. Epilepsy per se and/or seizures themselves promote sleep disruption and significantly affect the quality, quantity, and architecture of sleep. There are many causes of sleep disruption in patients with epilepsy, including inadequate sleep hygiene, coexisting sleep disorders, and circadian rhythm disturbances. Anti-epileptic drugs (AEDs) can also alter sleep in positive and negative ways, and these effects are independent of anticonvulsant actions. The end result of sleep disruption is excessive daytime sleepiness, worsening seizures, and poor quality of life. Screening for sleep disorders in the epilepsy population and appropriate intervention strategies will lead to overall improved quality of life and seizure control.

1. Introduction

Epilepsy and sleep disorders are considered by many to be common bedfellows. Sleep disorders frequently coexist in patients with epilepsy [1]. The complicated and reciprocal relationship between sleep and epilepsy is a topic that has been intriguing to physicians and researchers for many years [2]. Whether sleep affects epilepsy or epilepsy modifies sleep has been extensively evaluated [3]. But very little literature exists on the mutual interaction of epilepsy and sleep problems in the pediatric population.

According to a questionnaire based survey, the prevalence of subjectively reported sleep disturbance among adults with epilepsy (39%) was found to be significantly higher than among controls (18%) [4]. The prevalence of sleep disorders in children with epilepsy is under-recognized. In general, children with epilepsy experience alterations in total sleep, sleep architecture, sleep latency, and spontaneous arousals [5–7] with a higher incidence of sleep fragmentation and daytime drowsiness [8].

The etiology of sleep disruption in children with epilepsy is multi-factorial and includes factors such as epilepsy per se, seizure frequency, and the effect of anti-epileptic medications. A variety of treatable sleep disorders such as sleep disordered breathing (SDB), including obstructive sleep apnea (OSA), and periodic limb movements in sleep (PLMS) can be present in patients with epilepsy, leading to sleep fragmentation with resultant excessive daytime sleepiness (EDS), which in turn could lead to poor seizure control. Thus, sleep deprivation has seizure-provoking effects, while frequent seizures may in turn lead to sleep fragmentation. Furthermore, evidence suggests that the presence of seizures, even when they occur during wakefulness, can disrupt sleep, as can epilepsy per se [9]. Anti-epileptic drugs (AEDs) can alter sleep, both beneficially and detrimentally, and these effects appear independent of their anticonvulsant actions. AEDs may lead to weight changes in children as well [10]. The resultant sleep fragmentation along with obesity in itself may lead to EDS.

Not only quantity, but good quality sleep is important for optimal functioning in all people but is particularly essential in patients with epilepsy who may find themselves in a cycle of worsening seizures, further sleep disruption, and intractable epilepsy [11]. Treatment of sleep disorders in this population of children with epilepsy is likely to improve quality of life and daily functioning along with improved seizure control [11].

2. Sleep phenomena mimicking seizures

Several sleep phenomena may occur during nighttime, taking a wide variety of forms, and can mimic seizures. Sleep-related paroxysmal disorders in infancy and childhood represent a significant
challenge for the clinician, with the distinction of nocturnal epilepsy from non-epileptic sleep disorders often the primary concern [12]. Although in some patients, diagnosis is easy to achieve, at times a video/EEG recording of the episodes is required because of the similarity of the non-epileptic events to epileptic seizures [13].

With the International Classification of Sleep Disorders, 2nd edition (ICSD-2), developed by the American Academy of Sleep Medicine (AASM) in 2005, these disorders mimicking epilepsy can be broadly grouped into parasomnias, sleep-related breathing disorders, sleep-related movement disorders, and “others” [14]. In addition, certain sleep phenomenon can occur in wakefulness in the daytime, thus mimicking epilepsy.

These phenomena have been summarized in Table 1 [12,14].

2.1. Parasomnias

More than 80% of pre-school age children experience parasomnias, which are a big source of confusion in differentiating them from nocturnal seizures [15,16]. The various parasomnias have been summarized in a chapter in this issue. Features differentiating them from seizures will be addressed here and have been summarized in Table 2 [12,17].

<table>
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<th>Table 1</th>
<th>Paroxysmal disorders of sleep mimicking epilepsy (ASDA, 2005).</th>
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| 1. Parasomnias | a. Non-REM arousal disorders  
   i. Confusional arousals  
   ii. Sleep walking  
   iii. Sleep terrors  
 b. REM sleep disorders  
   i. Nightmares  
   ii. REM behavior disorder  
   iii. Parasomnia overlap syndrome  
   iv. Sleep paralysis  
 c. Others  
   i. Catathrenia (nocturnal groaning)  
 | 2. Sleep-related movement disorders  
 a. Periodic limb movements of sleep  
 b. Sleep bruxism  
 c. Nocturnal leg cramps  
 d. Rhythmic movement disorders  
 | 3. Other (non-parasomnia, non-movement disorders) paroxysmal nocturnal events  
 a. Sleep starts  
 b. Somniloquy  
 c. Benign sleep myoclonus of infancy  
 d. Nocturnal psychogenic non-epileptic seizures (PNES)  
 e. Nocturnal panic attacks  
 f. Sleep-related breathing disorders (obstructive sleep apnea)  
 g. Gastro-esophageal reflux  
 h. Narcolepsy (hypnagogic/hypnopompic hallucinations, sleep paralysis)  
 i. Sleep-epeneuresis  
 j. Newly recognized conditions  
   i. Excessive fragmentary myoclonus  
   ii. Propriospinal myoclonus at sleep onset  
   iii. Rhythmic sleep movements while falling asleep  
   iv. Alternating leg muscle activation during sleep and arousals  
| Daytime sleep episodes:  
1. Narcolepsy with cataplexy (mimicking atonic/tonic seizures with drop attacks)  
2. Episodic hypersomnia with narcolepsy (mimicking absence seizures, and post-ictal drowsiness)  
| Ref. [12].

2.1.1. Parasomnias predominately associated with non-REM sleep

Confusional arousals (sleep drunkenness), seen in young children, are characterized by sudden arousals usually from deeper NREM sleep stages, with disorientation and prolonged confusion on awakening, sometimes accompanied with complex behaviors, but without conscious awareness. They are very common, but under-recognized by non-sleep physicians, and are frequently misinterpreted as nocturnal seizures.

Somnambulism (sleep walking), seen in adolescents, consists of leaving the bed and performing complex activities such as walking, but with no memory of the event. It occurs during slow wave sleep and is of various duration and complexity. Some patients can be agitated during the episode [12].

Sleep terrors, seen in toddlers, are the most dramatic of the arousal disorders, characterized by prominent autonomic and affective features. The individual will suddenly arouse from deep sleep, usually with a “blood-curdling” scream, and appear pale and terrified. Often agitated behavior is seen, and sometimes the individual will attempt to leave the room; extreme agitation may result in injuries from jumping out of windows or falling down stairs [12]. They can usually be distinguished from seizures by their exclusive occurrence in sleep combined with the expression of extreme fear on the face. Multiple episodes per night, abnormal rhythmic movements, posturing of extremities, eye deviation, shorter duration of event but prolonged confusion, drooling, and tongue biting are suspicious for seizures [18]. However, it must be re-emphasized that occurrence only in sleep, expression of fear on the face, and accompanying aggressive behavior can also be seen in frontal lobe epilepsy (FLE) and has been further discussed under Section 3 in this article. In a recent paper, an Australian group attempted to differentiate parasomnias from FLE [17]. Elemental clinical features strongly favoring parasomnias included interactive behavior, failure to wake after event, and indistinct offset. While sleep stage at onset was discriminatory (82% of seizures occurred during stage 1 or 2 sleep, with 100% of parasomnias occurring from stage 3 or 4 sleep), ictal EEG features were less useful. Video analysis of parasomnias identified three principal behavioral patterns: arousal behavior (92% of events); non-agitated motor behavior (72%); distressed emotional behavior (51%).

Sleep deprivation, poor sleep hygiene, hypnotic use, or fragmented sleep (especially due to OSA) increases the frequency of these parasomnias [19]. Onset of events within 30 min of sleep-onset is suggestive of seizures, while onset at 2 h after sleep-onset is more suggestive of NREM parasomnias.

2.1.2. Disorders predominately associated with REM sleep

Nightmares, seen in toddlers and young children, consist of frightening dreams that often awaken the patient from sleep, and can be accompanied by agitation. There is generally full alertness upon awakening from a nightmare and intact recall of the dream experience. Unlike NREM phenomena like sleep terrors, there is usually no thrashing or ambulation. As REM sleep is preponderant during the second half of the night, nightmares tend to occur in the early hours of the morning [16].

REM behavior disorder: The presence of REM sleep without atonia, with prominent motor and behavioral manifestations associated with dreaming during REM sleep, is the key feature of a condition called REM sleep behavior disorder (RBD) [14], which may be idiopathic or associated with other neurological disease including narcolepsy and parkinsonian syndromes [20]. The bizarre movements, like kicking, punching, vocalization, and running accompanying these, can mimic nocturnal seizures. Injury to extremities during these events is common, while injuries during seizures are uncommon. Video-PSG may help in differentiating seizures from RBD. In children, narcolepsy remains the leading cause of RBD [21], though an important but unrecognized precipitating
factor is concomitant use of selective serotonin reuptake inhibitor (SSRI) antidepressants [22]. Other causes of RBD in children include cases of infiltrating tumors of the pons, post-excision of midline cerebellar astrocytomas, Tourette's syndrome, autism, hereditary quivering chin syndrome, traumatic brain injury, juvenile Parkinson disease, post-traumatic stress disorder, xeroderma pigmentosa, West syndrome, and olivopontocerebellar atrophy. Recently in children, the entity of “subclinical RBD,” with lack of REM atonia on PSG but without clinical features has been recognized [23]. In addition Ferri et al. used quantitative and computerized methods of analysis of the EMG signals and found significant PSG evidence of motor dyscontrol among patients with narcolepsy/cataplexy compared to controls. They used REM sleep atonia index as a marker, and found 38% of patients with narcolepsy/cataplexy to have REM sleep without atonia (RWSA) related to short lasting EMG activity [24]. Overall, subclinical RBD may be more common in narcolepsy, but remains unrecognized [21].

Overlap parasomnias have characteristics of both non-REM and REM sleep parasomnias and may be considered in the differential diagnosis of nocturnal seizures.

2.1.3. Other parasomnias
Catathrenia (nocturnal groaning) is a newly recognized parasomnia with unclear effects on sleep and life quality and which can mimic seizures [25]. It is characterized by repeated episodes of monotonous vocalization with prolonged expiration (episodes of bradypnea) occurring mostly in REM sleep. The hallmark of cata-

2.1.3.1. Sleep-related movement disorders. Periodic limb movements in sleep (PLMS) consist of repetitive cycles of rhythmic movement usually occurring in one or both legs but sometimes involving the arms, at five times per hour, 0.5–5 s in duration, in clusters of 4 or more leg movements, separated by 5–90 s [27]. Patients are usually unaware of the movements but may report frequent awakenings. They are rarely confused with seizures, but can cause daytime sleepiness. Actigraphy seems suitable in screening for PLMS over a few days time in an ambulatory setting [28].

Bruxism: consisting of teeth grinding and clenched movements of jaws during sleep. It is common in children and teenagers and may persist into adulthood. It is often seen in children with intellectual disabilities and with use of SSRIs. It may lead to sleep fragmentation with daytime hypersomnia and features similar to ADHD [29]. (It has also been recently described as a manifestation of temporal lobe seizures [30]).

2.1.3.2. Rhythmic movement disorders (RMD) of sleep. Jactatio Capitis (head banging) is characterized by rhythmic head banging and head rolling, along with body rocking, occurring in wakefulness,
during transition into sleep or during sleep. They are seen in children with intellectual disability, pervasive developmental disorders, or even in normal children. They can mimic nocturnal seizures. Reassurance of the parents is vital; rare cases need pharmacological intervention with use of clonazepam [31]. When RMD persist into childhood and beyond, possibility of behavioral, psychiatric, and attentional issues as comorbid conditions should be evaluated for [32].

2.1.3.3. Other paroxysmal events. Sleep starts, also known as hypnic jerks, are an extremely common phenomenon and are essentially physiologic in nature. They consist of brief myoclonic jerks, usually affecting the whole body at the transition of wakefulness and sleep. They are often associated with sensory phenomena, most commonly a sensation of falling. Caffeine, stimulants, stress, and excessive exercise may increase their frequency in some individuals [14]. When they become frequent and are accompanied with awakenings, they are seen in children with migraines, neurological impairments including cerebral palsy and epilepsy, and can mimic epileptic spasms [13].

Somniloquy (sleep talking) usually occurs during light NREM sleep or during arousals from deeper sleep, but occasionally arises during REM sleep [12]. It usually consists of single words or short sentences, usually with minimal affective content, and is sometimes associated with body movement [12]. Unlike seizures, speech during these episodes is random, while ictal speech tends to be stereotypical in a given individual. With somniloquy, there is usually a lack of abnormal body movements, drooling, tongue biting, or incontinence [17].

Benign sleep myoclonus of infancy is a common source of referral for video-EEG monitoring to rule out seizures. The myoclonus can be generalized or fragmentated, while the infant and EEG monitoring is always normal.

Nocturnal psychogenic non-epileptic seizures (PNES) are not uncommon in childhood and adolescents. Video-EEG monitoring confirms that they arise out of wakefulness even though they appear to be asleep and are characterized by bizarre, non-rhythmic movements, with waxing-waning character, and long durations. Common precipitating factors in children and teenagers include physical and sexual abuse [33].

Nocturnal panic attacks are characterized by brief awakening out of NREM sleep accompanied with choking sensation in the throat along with other respiratory symptoms and similar symptoms in the daytime consistent with panic attacks [34]. They are not uncommon in adolescent girls and video-EEG monitoring is often necessary in differentiating them from oribito-frontal nocturnal seizures.

Sleep-related breathing disorder (obstructive sleep apnea): symptoms of choking, gasping, and abnormal postures in sleep accompanying OSA are sometimes confused with nocturnal frontal lobe seizures. In some patients OSA can provoke seizures or be the primary reason for intractability of epilepsy [35,36]. Increasing evidence also suggests that OSA may trigger arousal parasomnias [37]. Interestingly, a recent paper found bursts of paroxysmal activity with embedded spikes on EEGs in children with OSA but not from children with habitual snoring, thus further complicating the issue of differentiating nocturnal events due to OSA from seizures. These bursts have been postulated to be responsible for the neuro-cognitive deficits observed in the daytime in children with OSA [38].

Narcolepsy is a chronic and potentially disabling rapid eye movement sleep disorder resulting from the dysregulation of sleep-wake cycle [22] that affects 0.03–0.16% of the general population including children in various ethnic groups [39].

Sleep paralysis is characterized by brief episodes of inability to move, generally occurring upon awakening, and relieved by touching or speaking to the child. Sleep paralysis can be accompanied by hypnagogic (during the transition from wakefulness to sleep) or hypnopompic (during the transition from sleep to wakefulness) hallucinations which consist of vivid visual or auditory experiences, usually of a benign content [14]. However, both of these symptoms can be unrecognized or misinterpreted by young children or their parents. They may seem to resemble nightmares in children and may be frightening and can also mimic nocturnal seizures. They can happen as an isolated phenomenon in variable frequency in normal children but can also occur in narcolepsy.

Gastro-esophageal reflux (Sandifer syndrome) can present with nocturnal arousals and bizarre postures and paroxysmal movements, along with torticollis in the daytime [40,41]. It presents typically between the ages of two months and five years. The episodic nature of attacks often results in misdiagnosis of paroxysmal dystonia or epilepsy [41].

Sleep enuresis can occur in NREM or REM and affects approximately 4–15% of school children [42]. As these episodes are typically unobserved, atypical characteristics of rhythmic body movements, tongue biting, or unexplained bruising warrant neuro-epileptologic evaluation and in some cases video-EEG monitoring to rule out unrecognized seizures [18].

2.1.3.4. Daytime episodes. Cataplexy is the presence of REM intrusion in wakefulness in patients with narcolepsy, with sudden but brief flaccid drop attacks in the daytime. These can mimic atomic seizures. Recently Serra et al. [43] have described features of cataplexy in children, emphasizing that isolated cataplexy without hypersomnia can present at the onset of narcolepsy in 10% of children. Atypical features are more common in childhood, with falls present in only 43% of cases. Most have only partial cataplexy involving face, eyelids, slurred speech, tongue thrusting, and blank stares. The usual triggers of emotion are not present and children are often unaware of these symptoms, thus making diagnosis difficult. The authors also describe “cataplectic facies” with a semi-permanent jaw and eyelid weakness. Video-PSG may be necessary to separate these drop attacks of cataplexy from the tonic/atonic seizures of Lennox Gastaut syndrome or Doose syndrome (myoclonic astatic epilepsy syndrome).

Thus, from the above description, the evaluation of sleep phenomena mimicking seizures involves taking a detailed history, encouraging family members to capture the events on home video, performing ambulatory EEGs, and often video-EEG or video-PSGs [44,45].

3. Sleep-related epilepsy syndromes

Although most seizure sub-types have the potential to occur during sleep or wakefulness, sleep has a well-documented association with specific epilepsy syndromes. The most important amongst these are nocturnal frontal lobe epilepsy, benign epilepsy with centro-temporal spikes, childhood epilepsy with occipital paroxysms, Landau–Kleffner syndrome and electrical status epilepticus during slow wave sleep [1–3,9,18,46]. Grand Mal seizures on awakening and generalized tonic clonic and myoclonic seizures with juvenile myoclonic epilepsy occur on awakening from sleep in the early morning.

3.1. Partial seizures: frontal lobe epilepsy

Partial seizures tend to occur in both sleep and wakefulness, although the semiology varies according to the site of onset. Clinically, onset from sleep is widely accepted as a clue to onset of the seizure from a frontal lobe focus [18].
Frontal lobe epilepsy (FLE) is more likely to occur during sleep than temporal lobe seizures [47,48]. The seizures may show bizarre semiology with posturing, ambulation, violent outbursts and complex behavior [49,50]. They are often misdiagnosed as OSA or a parasomnia due to the accompanying prominent choking or motor activity [18,46]. Only a third show clear epileptiform abnormalities on routine EEG [51]. Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE) is the first idiopathic epilepsy for which a genetic basis has been identified [52]. There is no difference between sporadic nocturnal FLE and ADNFLE in the clinical and neurophysiological findings. Paroxysmal arousals, episodic nocturnal wanderings (ENW), and nocturnal paroxysmal dystonia (NDP) are three characteristic manifestations of nocturnal FLE. ENWs can mimic sleep walking and confusional arousals but have accompanying motor patterns and an abnormal EEG not seen with parasomnias [53]. NDP, which was initially thought to be a parasomnia with dystonic posturing out of sleep, is now believed to be a variant of frontal lobe epilepsy from a deep focus, with minimal to no EEG changes during the event and normal EEGs in between attacks [54,55]. Episodes of NDP begin as a paroxysmal arousal, but are subsequently associated with more complex movements including bipedal automatisms, rhythmic twisting movements of the trunk and pelvis, vocalization, and tonic or dystonic posturing lasting less than a few minutes [12]. NDP are accordingly classified as hyperkinetic motor sub-type, or asymmetric bilateral tonic seizure sub-type [44].

Juvenile myoclonic epilepsy (JME) is a prototype of idiopathic generalized epilepsy and is characterized by a strong genetic predisposition [56] commonly presenting with early morning myoclonic jerks during adolescence. Generalized tonic–clonic seizures can occur independently or precede the myoclonus. These tend to occur in early morning hours shortly after awakening, with a second peak of occurrence in some patients in the early evening. Myoclonic seizures can be subtle and overlooked for many years as simple clumsiness [18]. These patients also have daytime absence seizures with staring spells which can mimic daytime sleep attacks. Patients may be exceedingly sensitive to sleep deprivation and alcohol consumption. Badawy et al. [57], very recently using transcranial magnetic stimulation to investigate the effect of diurnal variability on cortical excitability in patients with epilepsy, showed that cortical excitability increases early in the morning in patients with idiopathic generalized epilepsy, particularly in JME, but not in subjects with focal epilepsy or controls without epilepsy. This finding may explain the increased seizure susceptibility in these patients in the early morning. Labate et al. found early morning awake EEGs to be more useful in detecting generalized epileptiform activity in comparison with an afternoon session [58].

Benign epilepsy with centro-temporal spikes (BECT; Benign Rolandic Epilepsy) is the most common partial epilepsy syndrome in the pediatric age group, with an onset between age 3 and 13 years and remission in adolescence [59]. The typical presentation is a partial seizure with paresthesia and tonic or clonic activity of the lower face, associated with drooling and dysarthria. The seizures are mostly nocturnal, with 55–59% of patients having seizures exclusively during sleep [3]. EEG shows characteristic central and temporal spikes bilaterally but independently, potentiating during NREM sleep. The discharge rate is increased during drowsiness and light sleep as compared to the waking record, with no change in spike morphology. Despite the increased frequency of seizures and IEDs during sleep, the sleep architecture is not affected, and no sleep disruption is seen in these children. The response to medications is excellent, and the prognosis is universally benign from an epilepsy perspective. However, these children often have deficits in visuo-spatial short-term memory, attention and cognitive flexibility, picture naming, visuo-perceptual skills, and visuo-motor coordination. These deficits may be related to nocturnal spiking, but interestingly have not been associated in other epilepsy syndromes with daytime spiking and lack of nocturnal sleep potentiation of these spikes. Attempts at reducing the nocturnal spike index has resulted in improved cognition, albeit at the cost of significant side effects [60].

Landau–Kleffner syndrome (LKS) is an acquired disorder with epileptic aphasia in which children, usually 3–8 years of age, who have developed age-appropriate speech, experience language regression with verbal auditory agnosia, abnormal epileptiform activity, behavioral disturbances, and sometimes overt seizures [61]. Electrical status epilepticus in slow wave sleep (ESES) is primarily an EEG diagnosis and secondarily a clinical one, the principal criterion being the occurrence of spike wave (SW) complexes “continuously” during non-REM sleep but not during the awake state or in REM sleep [62]. The term continuous is applied only to EEG abnormalities with a spike index usually > 85% during SWS persistent on three or more recordings over a period of one month. There are several similarities between ESES and LKS. Both conditions demonstrate a normal EEG background during wakefulness, with generalized SW discharges or sometimes focal epileptiform activity. In ESES, however, discharges during sleep are generalized, while in LKS, SW activity is more temporally located. In ESES, epileptiform activity becomes virtually continuous during NREM sleep, such that it may be impossible to distinguish sleep stages [18,46].

Infantile spasms: example of a catastrophic epilepsy syndrome characterized by a triad of epileptic spasms of the body, variable extent of intellectual disability, and hypersynchronous EEG, with onset between ages 3 to 18 months. Interestingly, these spasms tend to cluster upon awakening in the morning [3].

Infantile variant of benign epilepsy of childhood with occipital paroxysms (BECOP; Panyiotopoulos syndrome) is an interesting benign epilepsy syndrome seen in children ages 2–6 years, characterized by prolonged periods of eye deviation and autonomic instability (temperature, heart rate, respiration, blood-pressure), hemiconvulsive and generalized tonic-clonic seizures in sleep, with vomiting on waking up. Inter-ictal EEGs show occipital spikes, while ictal EEGs show electrographic seizures emanating from the occipital region in sleep during these events [63].

4. The reciprocal relationship of sleep and epilepsy

4.1. Effect of sleep on epilepsy

4.1.1. Relationship of the sleep-wake state to epilepsy and inter-ictal epileptiform discharges (IEDs)

The occurrence of seizures during sleep has been noted since the time of Hippocrates and Aristotle [64]. In 1885, Gower found that 21% of patients had seizures solely during sleep, 42% only during the awake state, and 37% had seizures during both wake and sleep states [65]. The amount of baseline rhythmicity occurring in the brain differs considerably between the states of sleep and wakefulness. It is therefore not surprising that various seizure types begin preferentially in specific sleep states [9,18].

Crespen et al. [66] examined the occurrence of frontal lobe seizures (FLS) versus temporal lobe seizures (TLS) in 30 patients using 5 days continuous video-EEG monitoring. Sixty-one percent of FLS began during sleep, compared with only 11% with TLS. Bazil and Walczak [48] retrospectively examined video-EEG monitoring reports from 188 patients (1116 seizures) to look at patterns of seizure-onset in relationship to sleep and found that FLS were more likely to occur during sleep (37%) than temporal lobe seizures (26%). Durazzo et al. [67] retrospectively analyzed intracranial EEG recordings from 131 (669 seizures) consecutive adult subjects whose partial epilepsy was sufficiently localized for surgical resec-
tion. They showed that seizure occurrence in partial epilepsy is not random. Endogenous circadian rhythms and rhythmic exogenous factors likely play substantial roles in seizure occurrence. Most frontal and parietal lobe seizures occurred in the early morning (4–7 am); mesial and to a large extent lateral temporal lobe seizures occurred nearly equally during early morning (4–7 am) and late afternoon (4–7 pm), while occipital lobe seizures occurred much more commonly during late afternoon (4–7 pm). Similar findings have recently also been shown in children [68].

Sleep has a pronounced effect on secondary generalization of partial seizures, especially those of temporal origin. In the retrospective study of Bazil and Walczak [48], 35% of TLS during sleep underwent secondary generalization compared to 18% in wakefulness. FLS secondarily generalized at equal rates during sleep (22%) and wakefulness (20%). Based on these data, FLS began during sleep more often than temporal lobe seizures but TLS were more likely to secondarily generalize when they began during sleep.

IEDs are generally activated by NREM stages 3 and 4 in adults with focal epilepsy and relatively suppressed by REM sleep [69]. Using the change of log delta power as a measure of deepening sleep, Malow et al. [70] found that IEDs occurred more frequently as sleep deepened (N3 sleep). In contrast, focal IEDs that occur during REM sleep are more accurate for seizure localization as compared with other sleep states [71]. Interestingly, in children, several Italian studies using cyclical alternating patterns (CAP) and spectral analysis on the EEG have shown that IEDs in BECT and BECOP are more prevalent in stage 1 and 2 sleep, coinciding with sigma (12–16 Hz) activity, and occurrence of spindles, rather than with slow waves of sleep (0.5–4 Hz). These studies postulate that the neural mechanism underlying spindles also facilitate IEDs and that this is a maturational effect and an age dependent phenomenon. The immature brain combined with the hypersynchronizing functions of NREM sleep may lead to a regional hypexcitability of the cortex, thus facilitating thalamo-cortical volleys to transform from spindles into spikes [72–75].

Seizures in sleep also tend to occur during NREM sleep [3]. They are most frequently observed in stage 2 NREM sleep, followed by stage 1 and then stage 3 and 4 NREM sleep (in that order) [64]. Minecan et al. [76] examined seizure rates in various stages of sleep in epilepsy patients undergoing overnight video-EEG polysomnography (VPSG). A total of 55 patients having 117 seizures were included in that study. Ninety-five percent of seizures occurred in NREM sleep (61% stage 2, 20% stage 1, 14% stage 3 and 4) and only 5% in REM sleep. The authors concluded that both IEDs and seizures are facilitated by NREM sleep. While deeper stages of NREM sleep activate IEDs, lighter stages of NREM sleep promote seizures at least for a single seizure occurring per night in adults.

Seizure and spike rate in different stages of sleep in adults are shown in Fig. 1 [76].

4.1.3. Mechanisms influencing sleep and epilepsy

The neurophysiologic process involved in the deepening of NREM sleep may also facilitate both seizures and IEDs, although the exact level of sleep depth that is maximally facilitatory probably differs by age, epilepsy syndromes, and specific seizure subtypes and IEDs [76]. NREM sleep represents a state of synchronization between the brainstem reticular activating system, thalamus, and cortex (pyramidal neurons). The process of deepening NREM sleep is associated with reduction of the effect of acetylcholine, with progressive hyperpolarization of thalamo-cortical neurons [80]. Varying levels of hyperpolarization may facilitate IEDs and seizures. In contrast, REM sleep and wakefulness, two brain-activated behavioral stages, are opposed to the resting EEG-synchronized sleep [80]. REM sleep is characterized by inhibition of thalamocortical synchronizing mechanisms [81], a desynchronized EEG pattern, inhibition of spread of epileptiform discharges, and skeletal muscle paralysis.

Arousals from sleep result in transitions to lighter sleep, followed by a return to deeper levels of sleep. On the descent back to the deeper levels of sleep, seizures are more likely to occur. This model is consistent with work showing that patients with epilepsy have impaired sleep continuity, with more fragmentation of sleep, even in the absence of seizures [82]. Thus, seizures tend to occur more in sleep during cyclical alternating patterns (CAP), a pattern commonly seen with sleep fragmentation [83]. Therefore, patients with epilepsy may be more susceptible to the neurophysiologic changes associated with sleep stage transitions. This model may also explain why pathophysiologic processes that fragment sleep such as OSA have been associated with worsening seizure frequency and why treatment of these disorders may potentially improve seizure control [36,72,84]. In one series, those with medically refractory epilepsy and OSA were more likely to have seizures during sleep than those without OSA, supporting the premise that sleep fragmentation due to OSA facilitates seizures [18]. The literature also suggests that AEDs may exert their beneficial actions on seizures not only via direct effects on neuronal excitability, but also via stabilization of sleep and reduction of sleep transitions [59].

The exact mechanism of how sleep and sleep deprivation activate seizures is unclear and may be related to GABA modulation and/or the offset of adenosine with sleep onset [85]. Adenosine (AD) has long been thought to play a role in sleep, since caffeine, a major stimulant used around the world, was found to act as an antagonist at AD receptors. AD antagonists increase waking and decrease sleep EEG slow wave activity in humans and rodents [86]. Conversely, AD and its analogs increase sleep and enhance
slow wave activity in a way suggesting that AD could serve as an endogenous sleep promoting substance [85]. It is postulated that adenosine levels rise in the brain after prolonged wakefulness (thus signaling the brain of reduced brain energy levels that develop during wakefulness) and that sleep is induced as an energy restorative state. The inhibitory neuro-modulator and endogenous anticonvulsant adenosine is largely regulated by astrocytes and its key metabolite enzyme adenosine kinase (ADK) [87]. Adenosine acts as an anti-epileptogenic agent, while ADK acts as a pro-epileptogenic agent. Thus, at the transition of wakefulness to sleep, there is a dramatic drop in adenosine levels, along with high ADK levels, with lowered seizure threshold. Several studies support the ADK hypothesis of epileptogenesis; astrogliosis in the hippocampus is associated with epilepsy with up-regulation of ADK activity. This may have therapeutic implications in effective treatment of epilepsy via adenosine agonists or ADK antagonists [88].

Melatonin has been shown to enhance hippocampal excitability [89] and thus act as a pro-convulsant at high doses, but it may also have anti-epileptic properties in lower doses [90,91]. There have been conflicting reports on seizure control when prescribing melatonin for people with epilepsy [92–94]. The effects of ramelteon, a selective melatonin receptor agonist, were evaluated in two animal models of epilepsy, and the results of this study showed that it possesses anticonvulsant properties in a chronic epilepsy model [95].

In a recent study, decreased levels of hypocretin-1 in the CSF of patients with repetitive GTC seizures or status epilepticus have been demonstrated [95]. The results of this study suggest that the hypocretin-1 system deficiency may contribute to the typical somnolence after generalized tonic/clonic seizures. The exact mechanism of this observation is unclear.

4.2. Effect of epilepsy on sleep

Epilepsy per se and/or seizures themselves promote sleep disruption and significantly affect both the quality, quantity, and the architecture of sleep [45]. Patients with epilepsy generally have macro-structure sleep abnormalities such as increased number and duration of awakenings during sleep, reduced sleep efficiency, reduced or abnormal K complexes and sleep spindles, reduced and fragmented REM sleep, and increased stage shifts [96].

Seizures may acutely disrupt the sleep-wake state, with the clinical consequence of nocturnal insomnia and EDS [18,48]. Sleep is disrupted in patients with epilepsy on seizure free nights as well, when compared to non-epileptic controls. A possible explanation for this phenomenon could be that IEDs may cause sleep disruption, preventing normal progression though sleep stages [11].

Patients with seizures not only have a reduction in total sleep time but also REM sleep when compared with patients without seizures [45]. Reduced REM sleep is seen with seizures occurring during the day as well as at night and more so when seizures happen at night during sleep. Increased REM sleep, on the other hand, is seen with good seizure control [79].

Alterations in total sleep-time, sleep latency, and spontaneous arousals have also been reported in children with epilepsy [11]. Sleep abnormalities are more common in children with generalized seizures than in those with simple or complex partial seizures. Like in adults, REM sleep may be decreased by 50% in children with primary generalized tonic-clonic seizures [11].

The authors of an interesting study noticed several possible reasons for decreased REM sleep in patients with epilepsy. The first was that sleep was more disrupted, with more frequent awakenings and less time spent asleep, including in REM sleep. A second explanation was that seizures affect the circadian pattern responsible for REM sleep, thus delaying its onset. Seizures may also have a direct REM suppressant effect without disruption of circadian rhythms. Finally AEDs may alter REM sleep [97].

5. Potential causes of sleep disruption in epilepsy

There are many causes of sleep disruption in epilepsy patients, including inadequate sleep hygiene, coexisting sleep disorders, and circadian rhythm disturbances. Seizures themselves can disrupt sleep, even when they occur during wakefulness [97] (for details please read section: Effect of Epilepsy on Sleep). AEDs can also alter sleep in positive and negative ways, and these effects are independent of the anticonvulsant actions. The end result of sleep disruption is EDS, worsening seizures, and poor quality of life (Fig. 2).

6. Prevalence of sleep disorders in the epilepsy population

Prevalence of sleep complaints: Patients with epilepsy in general appear to have a greater prevalence of sleep disturbance than normal controls [45].

Stores et al. [98], using parental questionnaires, assessed sleep disturbances in 79 school children with epilepsy and 73 healthy control children. The authors found that children with epilepsy showed much higher rates of sleep disorders, particularly poor
quality sleep and anxieties about sleep in comparison with the normal controls. They also found a significant association between seizure frequency and anxieties about sleeping. Cortesi et al. [99] evaluated the presence of sleep problems and their association with behavioral and adjustment problems in children with idiopathic epilepsy and found that children with epilepsy had significantly more sleep problems than did both siblings and healthy controls. Within the epileptic group, children with current seizures complained more of sleep problems than did seizure-free children.

6.1. Polysomnographic findings in patients with epilepsy

A variety of treatable conditions have been shown to co-exist during sleep studies (polysomnography; PSG) in patients with epilepsy. Available literature describing PSG abnormalities in children with epilepsy is scarce but has been summarized in Table 3 [11,96,100–104].

Recently, we evaluated PSG abnormalities in a cohort of 40 children with epilepsy who underwent a sleep study for various sleep complaints [101]. Forty percent of the patients showed SDB, 42% primary snoring, 10% PLMS, and only 8% had a normal sleep study. Furthermore, children with poor control of epilepsy were more obese, had lower sleep efficiency, and higher arousal index in comparison with children with good seizure control or children free of seizures. We also compared the subgroup of children with epilepsy who were diagnosed with OSA with a subgroup of children with OSAS without epilepsy. Children with epilepsy with OSAS had longer sleep latency and higher arousal index in comparison with the non-epilepsy OSAS group. Even though the children with epilepsy had lower Apnea–Hypopnea Index (AHI) than children with uncomplicated OSAS, they desaturated more significantly with lower nadir oxygen desaturation. Whether the epilepsy syndrome, effects of AEDs, obesity, or upper airway anatomy contributed to this observation was unclear. We have also discussed our experience in scoring sleep stages during sleep studies in patients with frequent IEDs. All attempts must be made to differentiate NREM from REM sleep rather than to further attempt differentiation of N1–3 stages of NREM sleep. Data on sleep fragmentation caused due to partial versus generalized seizures in children are varied [11,96,100–104]. In our study, sleep fragmentation on PSGs was independent of seizure sub-types.

In a recent study, 970 healthy children from the general population and with no previous history of seizures or any other medical conditions underwent overnight PSG studies [105]. In 14 children (prevalence 1.45%), evidence of epileptiform activity was seen in the absence of any additional abnormality in the PSG. Epileptiform patterns found were either spike or spike and wave and were more prominent during NREM sleep, with 11 patients presenting with spike and wave patterns in the centro-temporal regions consistent with benign rolandic spikes, and 3 with generalized spike wave discharges. The authors concluded that the epileptiform activity in otherwise healthy children from the community is not uncommon and needs confirmation with formal EEGs. They also emphasize the need for PSG montages that include temporal leads and >2 standard EEG leads to facilitate the detection of epileptiform activity in children.

7. Breathing disorders in epilepsy

7.1. Obstructive sleep apnea (OSA)

OSA is particularly important, as it is frequently overlooked in patients with epilepsy, but appropriate treatment of OSA can result in reduced frequency or resolution of seizures. In some patients, OSA can also be the primary reason of intractability of epilepsy [35,36]. The postulated mechanisms explaining worsening of seizures with co-existing OSA could include:

Sleep loss: OSA is well known to cause sleep deprivation and sleep fragmentation. The effect of this sleep disruption deprives the patient from attaining restorative sleep and increases the time spent in stages of sleep vulnerable to seizure induction, thus overall reducing the threshold for seizures.

Oxygen desaturation: The effect of hypoxia on lowering the seizure threshold seems to be most prominent in the developing brain [106]. Hypoxia induces a hyperexcitable state in the immature hippocampus [107]. Animal studies have shown that hypoxia produces a profound effect on glutamate synapses and leads to the cascade of events that ends in cell death and reorganization that promotes epileptogenesis [108].

Many reports show that treatment of OSA by tonsillectomy and adenoidectomy or nasal continuous positive airway pressure (CPAP) have resulted in better control of the seizures secondary to improved sleep fragmentation [109]. In contrast, CPAP use has been responsible for precipitating parasomnias secondary to slow wave sleep rebound with use of CPAP. A recent paper also showed that use of CPAP in an otherwise normal child resulted in activating new onset of frontal lobe seizures, and the authors postulated mechanisms to explain the same [110].

On the other hand, the increased prevalence of OSA in patients with epilepsy may be from several etiologies:

Factors inherent to the epilepsy syndrome: Epilepsy may affect the regulation of respiration during sleep [111]. Foldvary-Schaefer et al. [112] described a case in which clinically significant OSA disappeared after left frontal lobe resection that produced a near seizure-free state. The pathophysiology of OSA in patients with epilepsy may be related to the effect of frequent IEDs and/or seizures altering upper airway control. Abnormal upper airway anatomy in epilepsy with onset in early childhood may be another explanation.

Factors associated with the treatment of the epilepsy: AEDs may lead to obesity which is a commonly accepted risk factor for OSA [113]. VNS affects respiration during sleep and has been shown to worsen preexisting OSA [114] (for more details please read the section: Effect of Epilepsy Treatment on Sleep).

7.2. Central sleep apnea (CSA)

CSA during epileptic seizure may be multi-factorial [115]. The link between CSA and seizures is reciprocal and complex. CSA may trigger a seizure because of the hypoxia caused by the central apnea reducing the seizure threshold [97]. On the other hand, seizures may trigger a CSA [115] or CSA may be an event at the end of the seizure [116].

Tezer et al. [115] recently documented the epileptic origin of ictal CSA in patients with right temporal and parasagittal epilepsy with EEG-video monitoring and placement of both noninvasive and invasive electrodes and concomitant PSG recording. The authors emphasize the importance of an epileptic origin of CSA in the differential diagnosis of breathing abnormalities.

Blum et al. [117] examined the occurrence of hypoxemia in adults with partial seizures. During long-term video/EEG monitoring (LTM), patients underwent monitoring of oxygen saturation using a digital SpO2 (pulse oximeter) transducer. The results of this study showed that partial seizures may be associated with prominent oxygen desaturations. The comparable duration of each seizure and its subsequent desaturation suggest a close mechanistic (possibly causal) relationship. SpO2 monitoring thus provides an additional measure of seizure detection. These observations also raise the possibility of ictal ventilatory dysfunction playing a role
in certain cases of sudden unexpected death in epilepsy population (SUDEFP) in adults with partial seizures [118].

O’Regan and Brown [116] examined changes in cardiac and respiratory function that occurred during 101 seizures (40 partial, 21 generalized tonic/clonic, and 40 absences) in 37 children and found that partial seizures were frequently associated with significant respiratory abnormalities (tachypnea in 56%, apnoea in 30%, frequent respiratory pauses in 70%, and severe hypoxemia in 40%). Catastrophic apnoea with severe hypoxemia necessitating repeated cardiopulmonary resuscitation could be the presentation of a seizure with epileptic activity on the EEG preceding the apnoea.

A recent study linked occurrence of central apneas with hypoxemia to spread of seizures to the contralateral side in patients with temporal lobe epilepsy, thus suggesting that spread of seizures from both temporal lobes to the respiratory centers in the brain stem may be necessary to induce sleep related respiratory disturbances [119].

Several possible mechanisms could explain how seizures can cause breathing abnormalities:

- Partial seizures may spread from the limbic structures and the temporal lobes to the brainstem respiratory center, inducing a CSA
- Generalized tonic seizures may cause diaphragmatic and glottis spasm thus inducing CSA
- Hypoventilation and/or ventilatory instability may occur during the seizure with resultant CSA
- Hyperventilation during seizures leads to CO2 washout with post arousal prolonged CSA [120]
- Cardiac autonomic instability with tachycardia may occur during seizures
- Components of OSA may occur in addition to CSA during a seizure
- Lying prone with resultant suffocation
- Neurogenic pulmonary edema

Overall, these possibilities may explain mechanisms for SUDEFP.

8. Effect of epilepsy treatment on sleep

Anti-epileptic drugs (AEDs): The effects of AEDs on sleep have been studied independent of seizures showing both detrimental and beneficial effects. AEDs can induce sedation or insomnia [45]. AEDs can also affect sleep architecture. Several studies have shown that some AEDs can produce sleep stability [121]. This naturally poses the question of whether the improvement in sleep patterns is a direct consequence of the use of the AED or the consequence of a suppression of epileptic manifestations. It is possible that sleep improvement plays a role in the therapeutic effects of these drugs. The beneficial effect may be expressed as the occurrence of more regular cycles of sleep. The restoration of sleep stability in successfully treated patients may be seen as a decrease in time spent awake during the sleep cycle after the use of an AED and may be a consequence of an increased arousal threshold

Table 3

<table>
<thead>
<tr>
<th>Population sample</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kotagal et al. [102]</td>
<td>Nine patients with spastic quadriaparesis and epilepsy with a mean age of 36.7 months</td>
<td>-</td>
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<tr>
<td>Maganti et al. [100]</td>
<td>Eleven children with primary generalized epilepsy who were seizure free and ages 5–18 years old</td>
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<tr>
<td>Malow et al. [103]</td>
<td>Sixteen subjects with mean age 33.6 ± 11.1 with medical refractory seizures who underwent a PSG and MSLT before and after 3 months of VNS</td>
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<tr>
<td>Nunes et al. [96]</td>
<td>Seventeen children with partial refractory epilepsy</td>
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<td>Becker et al. [11]</td>
<td>Fourteen children with epilepsy compared with patients with diagnosed OSA</td>
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<tr>
<td>Nagarajan et al. [104]</td>
<td>Seven children with epilepsy on VNS</td>
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<tr>
<td>Kothare et al. [101]</td>
<td>Forty children with epilepsy Eleven children with OSAS without epilepsy</td>
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</table>

OSA-obstructive sleep apnea; IED-inter-ictal discharges; CP-cerebral palsy; REM-rapid eye movement; CBCL-child behavior checklist; RPCS-respiratory pattern changes in sleep; PSG-polysomnography; QOL-quality of life; MSLT-multiple sleep latency tests; MSL-mean sleep latency; VNS-vagal nerve stimulator.
9. Conclusions

We have summarized here the salient relationship between epilepsy and sleep in children. Sleep fragmentation with resultant EDS is very common in the epilepsy population. The commonest treatable comorbidity associated with epilepsy is OSA. Awareness of these sleep comorbidities along with effective screening measures to appropriately detect and treat them will lead to overall improved seizure control, sleep quality, daytime functioning, and quality of life. AEDs can be contributors and effective treatment measures for sleep fragmentation.

References


Table 4

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sleep complaint</th>
<th>Sleep efficiency</th>
<th>TST</th>
<th>SL</th>
<th>Arousals</th>
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<th>% Stage 2</th>
<th>% SWS</th>
<th>% REM</th>
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TST = total sleep time; SL = sleep latency; SWS = slow wave sleep; REM = rapid eye movement; S = sleepiness; I = insomnia; ↑ = increase; ↓ = decrease; 0 = no change; ↑ = unknown.


