Abstract: The distinction between epileptic and nonepileptic events out of sleep may represent a significant challenge to the pediatrician. It is known that sleep can facilitate epileptic activity and that seizures in sleep tend to occur during specific sleep stages. Certain epilepsy syndromes have a well-documented and strong association with sleep and can present with a variety of bizarre behaviors and motor activity. Disorders that may present with nocturnal nonepileptic paroxysmal events may include not only sleep-related disorders, but also psychiatric/behavioral conditions. Benign paroxysmal phenomena with unrelated etiology, and nonepileptic disorders, these phenomena, especially when involving complex motor activity, such as that observed in parasomnias, nocturnal panic attacks, and rapid eye movement behavior disorders, may be difficult to differentiate from seizures. Moreover, there is increasing awareness that certain sleep disorders, such as sleep-disordered breathing, may coexist with epilepsy. There are several clinical and electrophysiological features that allow an accurate diagnosis, and diagnostic tools such as video-EEG polysomnography may be essential.

Key Words: Nocturnal events, Seizures, Children.


EPILEPTIC PAROXYSMAL EVENTS OUT OF SLEEP IN CHILDREN

There is clinical and scientific evidence supporting the notion that the sleep–wake cycle is regulated by different mechanisms, which can affect the expression of epilepsy. During nonrapid eye movements (REM) sleep, the thalamic nuclei provide bilateral synchronized afferent inputs to the cortex, potentially leading to the activation of ictal foci in susceptible patients (Doming et al., 1986; Steriade, 2005). Conversely, REM sleep is characterized by inhibition of the thalamocortical synchronization mechanisms and inhibition of interhemispheric networks preventing the spread and generalization of epileptiform discharges (Shouse et al., 1989). Both interictal epileptiform discharges (IEDs) and ictal epileptiform activity are facilitated during non-REM sleep (Ferrillo et al., 2000). Specifically, IEDs are activated during slow-wave sleep (SWS), whereas seizures are promoted during lighter non-REM sleep stages (Ferrillo et al., 2000; Malow et al., 1998; Minecan et al., 2002). Certain epilepsies, especially primary generalized epilepsy syndromes, are known to be suppressed during REM sleep (Minecan et al., 2002). A certain timing of seizure in relation to sleep–wake cycle and to the night–day circadian rhythms is also observed in many childhood epilepsy syndromes. Childhood epilepsy syndromes that are known to be affected by sleep–wake cycle are described below.

Frontal Lobe Epilepsy

Frontal lobe seizures are characterized by a spectrum of manifestations ranging from brief arousals to complex behavior and motor activity including ambulation, and violent outbursts (Provini et al., 2000a,c). Given these features, frontal lobe seizures may be misdiagnosed with other sleep disturbances including night terrors and REM behavior disorder (RBD) (Provini et al., 2000a,c). Choking sensation may be a prominent feature of nocturnal seizures, and therefore may be often misdiagnosed as obstructive sleep apnea (OSA) (Provini et al., 2000c). Only one third of patients with frontal lobe seizures show epileptiform abnormalities on routine EEG; long-term video-EEG monitoring remains the gold standard for the diagnosis (Ryvlin et al., 2006). Studies on video-EEG polysomnography (PSG) have also shown that frontal lobe seizures may often be unrecognized and underreported (Provini et al., 1999).

Paroxysmal nocturnal dystonia has been regarded as a variant of FLE, arising from a deep brain focus with only minimal to absent EEG changes during the event and normal EEGs in between attacks (Provini et al., 2000b). Episodes of paroxysmal nocturnal dystonia begin with an abrupt arousal, followed by complex motor features including bipedal automatism, rhythmic twisting movements of the trunk and pelvis, vocalization, and tonic or dystonic posturing lasting approximately 1 to 2 minutes (Provini et al., 2000b). Episodic wandering is characterized by an arousal, followed by bizarre motor activity followed eventually by ambulation (Plazzi et al., 1995).

Juvenile Myoclonic Epilepsy

Juvenile myoclonic epilepsy is an idiopathic generalized epilepsy syndrome, commonly presenting during adolescence. Myoclonic jerks, especially after morning awakenings, are commonly a presenting feature (Badawy et al., 2009). 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. Predisposition to seizures during the morning hours may be related to increased motor cortical excitability early in the morning (Badawy et al., 2009). Myoclonic seizures can be subtle and overlooked for many years as simple clumsiness (Bazil, 2004). Staring spells are also
Benign Epilepsy With Centrotemporal spikes

Benign epilepsy with centrotemporal spikes, also known as benign rolandic epilepsy, is the most common partial epilepsy syndrome in children. Typically, benign epilepsy with centrotemporal spikes has onset between the age of 3 and 13 years with remission during adolescence (Baglietto et al., 2001; Wirrell, 1998). Seizures almost exclusively occur during the night and approximately 60% of patients report seizures exclusively during sleep (Baglietto et al., 2001). Seizure semiology in benign epilepsy with centrotemporal spikes includes paroxysms of stereotyped focal motor seizures and eye deviation. Video-EEG monitoring clearly reveals the diagnosis. The pathognomonic EEG feature of benign epilepsy with centrotemporal spikes is central and temporal spikes bilaterally, but independently, potentiating during non-REM sleep (Baglietto et al., 2001; Laub et al., 1992). The epileptic discharge rate is higher during drowsiness and light sleep when compared with the waking record, with no change in spike morphology (Laub et al., 1992). Several studies have shown that despite the increased frequency of seizures and IEDs during sleep, there is no disruption of sleep architecture (Baglietto et al., 2001; Bruni et al., 2010; Laub et al., 1992).

Benign Epilepsy of Childhood With Occipital Paroxysms

Infantile variant of benign epilepsy of childhood with occipital paroxysms, or Panayiotopoulos syndrome, presents in children between the age of 2 and 6 years (Capovilla et al., 2009). Seizure semiology includes prolonged periods of eye deviation and autonomic instability (with dysregulation of temperature, heart rate, respiration, and blood pressure) during sleep, and vomiting at awakening (Michael et al., 2010). Although the semiology of these events may resemble nonepileptic paroxysmal attacks such as panic attacks, sleep terror, and other parasomnias, routine EEG may be sufficient for the diagnosis of benign epilepsy of childhood with occipital paroxysms. Interictal EEG typically shows discharges in the occipital region (Capovilla et al., 2009; Michael et al., 2010).

Infantile Spasms

Infantile spasms, as seen in West syndrome, consist of epileptic spasms of the body, which may occur in clusters in the morning on awakening (Rodriguez and Kuzniecky, 2008; Zupanc, 2009). They present during infancy, generally in children up to 18 months of age (Zupanc, 2009). They may need to be differentiated from benign myoclonic phenomena associated with sleep, such as sleep starts (hypnic jerks), benign sleep myoclonus of infancy, and benign myoclonic epilepsy of infancy. However, children with infantile spasm show a variable extent of brain pathologic assessment and intellectual disability, which frequently point to an early diagnosis. Furthermore, EEG studies in West syndrome show a characteristic signature of hypsarrythmia (Zupanc, 2009).

Landau–Kleffner Syndrome and Electrical Status Epilepticus in Slow-Wave Sleep

Landau–Kleffner syndrome, also known as epileptic aphasia, is an acquired disorder usually presenting at ages 4 to 6 years with language regression (with verbal auditory agnosia) and seizures. Electrical status epilepticus in SWS is a syndrome characterized by the occurrence of continuous spike-wave complexes during SWS (seen during at least 85% of non-REM sleep), but not during the awake state or in REM sleep (McVicar and Shinnar, 2004). No primary sleep disturbance has been reported except for difficulty in waking up in morning (McVicar and Shinnar, 2004). Landau–Kleffner syndrome and electrical status epilepticus in SWS have been further discussed in a separate chapter in this issue.

NONEPILEPTIC PAROXYSMAL EVENTS OUT OF SLEEP IN CHILDREN

Nonepileptic paroxysmal events out of sleep in children are relatively common events that need to be differentiated from epileptic events. Disorders that may present with nocturnal nonepileptic paroxysmal events may include not only sleep-related disorders per se but also psychiatric/behavioral conditions, “benign” paroxysmal phenomena with unrelated pathologic assessment, and noneurologic pathologies (Crompton and Berkovic, 2009; Derry et al., 2006). A summary of these events is presented in Table 1. Sleep-related disorders have been grouped according to the International Classification of Sleep Disorders (American Academy of Sleep Medicine, 2005).

Parasomnias

Parasomnias are extremely common in preschool age children, reaching a prevalence of approximately 80% (Stores, 2009). Together with epileptic seizures, they represent the major disorders in the differential diagnosis for paroxysmal nocturnal events (Derry et al., 2006, 2009). Parasomnias can be characterized by bizarre behaviors and complex motor activity; differentiating these from epilepsy may be difficult. In both parasomnias and seizures, we can observe (1) oromotor automatisms and bruxism; (2) amnestic-type behaviors, ranging from the classic bicycling activity to episodic wanderings, and somnambulism; and (3) various sleep-related events such as arousals from sleep and violent behavior (Tassinari et al., 2009).

The major clinical features differentiating parasomnias from nocturnal seizures are presented in Tables 2 and 3 (Derry et al., 2006, 2009; Provini et al., 1999; Zuconi and Ferrini-Strambi, 2000). In general, clinical features highly favoring parasomnias include interactive behavior, failure to wake up after event, and indistinct offset. Sleep stage at onset may help the differentiation: onset during stage 1 or 2 sleep suggests seizures, whereas onset in SWS and REM sleep suggests parasomnias (Derry et al., 2006, 2009). Onset of events within 30 minutes of sleep onset is suggestive of seizures, whereas onset at 2 hours after sleep onset is more suggestive of non-REM parasomnias (Derry et al., 2006, 2009).

Non-REM Arousal Disorders

Confusional Arousals

Confusional arousals (sleep drunkenness) are characterized by sudden arousals, disorientation, and prolonged confusion, sometimes associated with complex behaviors, but never with conscious awareness (Stores, 2009). They are very common, especially in young children, but under-recognized by non-sleep pediatricians, and frequently misinterpreted as nocturnal epileptic events (Stores, 2009).
Somnambulism

Somnambulism (sleep walking) is common among the adolescent population and consists of episodes of complex and elaborate activities including walking, but without recollection of these events (Hughes, 2007). Agitation has been described in association with sleep walking (Stores, 2009).

Sleep Terrors

Sleep terrors are typically seen in toddlers and are characterized by sudden arousals with a loud and inconsolable scream (Mason and Pack, 2005). The toddler seems pale and terrified. There is no awakening and the child usually falls asleep and does not recall the event at a later time (Mason and Pack, 2005). The distinction between sleep terrors and epileptic events is challenging. 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 (Derry et al., 2006). Sleep terrors occur only in sleep and the facial expression of extreme fear is fairly pathognomonic of this condition. However, similar semiology have also been described in FLE (Crespel et al., 1998).

Parasomnias Associated With REM Sleep

Nightmares

Nightmares consist of frightening dreams that can awaken the child from sleep and can be associated with significant agitation. Unlike sleep terrors, there is generally full alertness on awakening from a nightmare and full recall of the dream afterward (Kotagal, 2008). They are commonly seen in toddlers and young children. As REM sleep predominates in the second half of the night, nightmares are typically seen in the early hours of the morning (Kotagal, 2008).

REM Behavior Disorder

REM behavior disorder is characterized by motor and behavioral manifestations associated with dreaming during REM sleep (Stores, 2008). The presence of bizarre movements and complex behavior, including laughing, talking, moaning, punching, kicking, and running can mimic epileptic events (Stores, 2008). Injury to

### TABLE 1. Non epileptic Paroxysmal Events Out of Sleep in Children

<table>
<thead>
<tr>
<th>Parasomnias</th>
<th>Non-REM arousal disorders</th>
<th>Sleep walking</th>
<th>Sleep terrors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasomnias associated with REM sleep</td>
<td>Nightmares</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other parasomnias</td>
<td>Catathrenia (nocturnal groaning)</td>
<td>Sleep enuresis</td>
<td>Exploding head syndrome</td>
</tr>
<tr>
<td>Sleep related hallucinations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep related movement disorders</td>
<td>Periodic limb movements of sleep</td>
<td>Sleep bruxism</td>
<td>Nocturnal leg cramps</td>
</tr>
<tr>
<td>Sleep-related breathing disorders (OSA)</td>
<td>Psychiatric and behavioral disorders</td>
<td>PNEs</td>
<td>Nocturnal panic attacks</td>
</tr>
<tr>
<td>Isolated “benign” paroxysmal nocturnal events</td>
<td>Sleep starts (hypnic jerks)</td>
<td>Benign sleep myoclonus of infancy</td>
<td>Excessive fragmentary myoclonus</td>
</tr>
<tr>
<td>Propriospinal myoclonus at sleep onset</td>
<td>Hypnagogic foot tremor</td>
<td>Alternating leg muscle activation during sleep</td>
<td>Nonneurological paroxysmal events</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**TABLE 2. Major Clinical Features Helping the Differentiation Between Parasomnias and Nocturnal Seizures**

<table>
<thead>
<tr>
<th>Parasomnias</th>
<th>Nocturnal Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2 episodes per night</td>
<td>&gt;3 episodes per night</td>
</tr>
<tr>
<td>1–4 episodes per month</td>
<td>&gt;10 episodes per month</td>
</tr>
<tr>
<td>Episodes occur during REM or SWS</td>
<td>Episodes occur during stage 1 and 2</td>
</tr>
<tr>
<td>Episodes occur more likely after 90 minutes of sleep onset</td>
<td>Episodes may occur at any time of the night</td>
</tr>
<tr>
<td>Episodes lasts up to 30 minutes</td>
<td>Episodes lasts up to 1–2 minutes</td>
</tr>
<tr>
<td>Variable movements and actions</td>
<td>Stereotyped movements</td>
</tr>
<tr>
<td>Physical and verbal interaction</td>
<td>Rare physical and verbal interaction</td>
</tr>
<tr>
<td>Failure to fully arouse after the event</td>
<td>Postictal confusion may be present but the patient generally is fully arousable after the event</td>
</tr>
<tr>
<td>Common positive family history</td>
<td>Positive family history less common</td>
</tr>
</tbody>
</table>

**TABLE 3. Clinical Features Which Can Be Used for Identification of Parasomnias Versus NFLE**

<table>
<thead>
<tr>
<th>Parasomnias</th>
<th>Internal or external trigger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical features strongly suggestive of parasomnias</td>
<td>Rolling over in bed, changing position</td>
</tr>
<tr>
<td>Yawning</td>
<td>Waxing and waning pattern</td>
</tr>
<tr>
<td>Physical/verbal interaction</td>
<td>Indistinct offset</td>
</tr>
<tr>
<td>Failure to fully arouse after event with complex behavior</td>
<td>Discordance between severity and duration of reported versus recorded event</td>
</tr>
<tr>
<td>Clinical features that do not discriminate between parasomnias and NFLE</td>
<td>Sitting, standing, or walking</td>
</tr>
<tr>
<td>Preceding “normal” arousal</td>
<td>Brief arousals (up to 10 seconds) without definite semiological features of epilepsy</td>
</tr>
<tr>
<td>Fearful emotional behavior</td>
<td>Manipulation of nearby objects</td>
</tr>
</tbody>
</table>

**References:** Derry et al., 2006; Provini et al., 1999; Zucconi et al., 2000. REM, rapid eye movements of sleep; SWS, slow wave sleep.
extremities during these events is common, whereas injuries during seizures are less common. Video-PSG may help in differentiating seizures from RBD. It can be idiopathic or associated with other neurologic diseases including narcolepsy and Parkinsonian syndromes (Boeve, 2010; Wierzbicka et al., 2009). In children, narcolepsy remains the leading cause of RBD (Nevsimalova et al., 2007). A precipitating factor may be the use of selective serotonin reuptake inhibitors (Frascher et al., 2010). The diagnosis of RBD is generally confirmed with PSG, with the absence of chin EMG atonia during REM sleep (Boeve, 2010). In general, there is the presence of normal non-REM sleep architecture (Schenck et al., 2003). PSG shows that events of RBD occur during REM sleep, and this represents a major differentiating finding from nocturnal seizures. In general, the absence of REM sleep atonia and the occurrence of the episodes out of REM sleep are enough for a definite diagnosis of RBD.

Overlap Parasomnias

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

Other Parasomnias

Sleep Enuresis

Sleep enuresis more commonly known as bedwetting, refers to the lack of ability to maintain urinary control during sleep. Bedwetting can be a feature of a nocturnal seizure, and parents may hear nocturnal sounds associated with abnormal movements accompanying the bed wetting (Neveus, 2009). PSGs are generally not necessary to differentiate sleep enuresis from nocturnal epilepsy. As these episodes are typically unwitnessed, atypical-associated features of rhythmic body movements, tongue bite, or unexplained bruising warrant neurologic evaluation, and in some cases, video-EEG monitoring was performed to rule out epileptic events.

Explooding Head Syndrome

Explooding head syndrome has been rarely described in children. One experiences a loud bang or explosion noise in the head, resulting in total wakefulness, panic, or being emotionally upset (Evans, 2006). Attacks tend to occur at the onset of sleep.

Catathrenia

Catathrenia (nocturnal groaning) is characterized by monotonous vocalization with prolonged expiration (episodes of bradynea) occurring mostly out of REM sleep (Ramar et al., 2008). The most important feature that helps distinguishing catathrenia from other parasomnias is the occurrence of the episodes out of REM sleep, which is a major differentiating finding from nocturnal seizures. In general, catathrenia has not been described in children yet.

In evaluating a child presenting with paroxysmal nocturnal events, the pediatrician should take into account that sleep deprivation, poor sleep hygiene, hypnotic use, or fragmented sleep, especially secondary to OSA, can increase the frequency of both parasomnias and seizures (Owens et al., 1997; Vaughn and D’Cruz, 2003).

The diagnosis of parasomnias and epilepsy becomes even more challenging, when these disorders coexist. Parasomnias in patients with NFLE have been described (Derry et al., 2006). Furthermore, parasomnias can also be seen in relatives of NFLE patients, suggesting a possible shared pathogenic mechanism (Bisulli et al., 2010). A recent case–control family study concluded that arousal disorders and nightmares are more frequent among NFLE proband relatives than controls, and arousal disorders (including bruxism) are more frequent among NFLE probands than controls (Bisulli et al., 2010). The higher frequency of these parasomnias in NFLE families suggests an intrinsic mechanism between parasomnias and NFLE (Bisulli et al., 2010). An abnormal arousal system, likely cholinergic, has been implicated as a possible shared pathophysiologic mechanism (Bisulli et al., 2010; Derry et al., 2009).

Sleep-Related Movement Disorders

Periodic Limb Movements of Sleep

Periodic limb movements of sleep occur mostly during transition into sleep and consist of repetitive cycles of rhythmic movement of one or both legs, 0.5 to 2 seconds in duration, in clusters of four or more (American Academy of Sleep Medicine, 2005). At least five movements per hour have to be observed to meet the diagnostic criteria (American Academy of Sleep Medicine, 2005). Children are usually unaware of the movements but these movements are generally reported by the parents. They are rarely confused with seizures, but can cause daytime sleepiness. Actigraphy is useful in screening for periodic limb movements of sleep over a few days of time (Ancoli-Israel et al., 2003), although PSG remains the gold standard when differentiation from seizures is needed.

Sleep Bruxism

Sleep bruxism consists of teeth grinding and clenching movements of jaws during sleep. It is common in children and teenagers. Risk factors include intellectual disabilities and use of selective serotonin reuptake inhibitors (Bloomfield and Shatkin, 2009; Ellison and Stanziani, 1993). It may lead to sleep fragmentation with daytime sleepiness and hyperactivity and attention issues similar to attention deficit hyperactivity disorder (Silvestri et al., 2009). Exceptionally, a teeth-grinding event may be a manifestation of an epileptic-related motor event (Meletti et al., 2004).

Jactatio Capitis

Jactatio Capitis (headbanging) is characterized by rhythmic forward and backward motions of the head, which may be accompanied by body rocking, occurring during transition into sleep or during sleep. Risk factors predisposing to headbanging are intellectual disability and pervasive developmental disorders, although they are also seen in normal children (de Raeymaecker, 2006). They can resemble nocturnal seizures. They tend to occur during the first part of the night (Kohyama et al., 2002). In addition, the episodes of headbanging tend to be more prolonged than epileptic events and can last for up to 1 hour. Some cases may need pharmacological intervention with use of benzodiazepines such as clonazepam (Su et al., 2009).

Narcolepsy

Narcolepsy is a chronic REM sleep disorder affecting approximately 0.03% to 0.16% of the general population including children from various ethnic groups (Nevsimalova, 2009). Nocturnal symptoms such as hypnogogic/hypnopompic hallucinations and sleep paralysis need to be differentiated from epileptic events. Sleep paralysis is characterized by brief episodes of inability to move, generally occurring on awakening, and, unlike epileptic events, is relieved by touching or speaking to the child. Sleep paralysis can be accompanied by hypnogogic (transitioning from wakefulness to sleep) or hypnopompic (transitioning from sleep to wakefulness) hallucinations that consist of vivid visual or auditory experiences, thus making differentiation from nocturnal seizures difficult (Macleod et al., 2005).
Anticipatory anxiety and fear while going to sleep is indicative of panic attacks rather than epileptic seizures (Craske and Barlow, 1989). Additionally, they are more commonly seen in adolescent girls (Craske and Barlow, 1989). Video-EEG monitoring may be useful when the diagnosis remains uncertain.

**Nonneurologic Paroxysmal Events**

**Sandifer Syndrome**

Sandifer syndrome (Gastroesophageal Reflux) refers to spasmatic torsional dystonia with arching of the back and rigid opisthotonic posturing, mainly involving the neck, back, and upper extremities, associated with symptomatic gastroesophageal reflux. It is most commonly seen in infancy, with a peak at age 1 to 4 months, although it can affect children of all ages (Orenstein, 2000). The episodic nature of attacks often results in misdiagnosis of epilepsy. During these movements, the infant usually becomes very quiet or, less commonly, very fussy and cries. Typically, fussiness and evident discomfort is most commonly observed as the posture abates. Some infants may manifest evidence of respiratory tract irritation as well, including cough, wheezing, and stridor (Orenstein, 2000).

**Sleep-Related Breathing Disorders**

Choking, gasping, motor activity, and abnormal postures during sleep accompanying OSA may be confused with nocturnal frontal lobe seizures. PSG with full EEG montages are becoming common practice tools in tertiary care centers and represent the gold standard for the differentiation of sleep-disordered breathing (SDB) from nocturnal epilepsy. However, one should keep in mind that SDB and epilepsy may coexist (see below) (Malow et al., 1997, 2000b, 2003).

**COEXISTENCE OF SLEEP DISORDERS AND EPILEPSY**

**Effect of Seizures and Epilepsy on Sleep Physiology**

It is well accepted that epilepsy and seizures can cause sleep disruption and thus affect significantly quality, quantity, and architecture of sleep. Patients with epilepsy generally have 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 changes (Malow et al., 2000b; Nunes et al., 2003; Touchon et al., 1991). Sleep abnormalities are more common in children with generalized seizures than in those with simple or complex partial seizures (Becker et al., 2003). Seizures can directly disrupt sleep, but patients with epilepsy have poor sleep efficiency and quality also on seizure-free nights (Bazil et al., 2000). It has been postulated that this phenomenon may be related to the effects of AEDs on preventing normal progression though sleep stages (Becker et al., 2003).

Patients with seizures experience decreased REM sleep, and increased REM sleep is seen with good seizure control (Bazil et al., 2000). REM sleep may be decreased by 50% in children with primary generalized tonic–clonic seizures (Becker et al., 2003). This may be related to seizure-related circadian patterns disruption, direct REM suppressant effect of seizures, and the effects of AEDs on REM sleep (Bazil, 2008).
Sleep Breathing Disorders in Children With Epilepsy

Obstructive Sleep Apnea

There is little information on PSG findings in children with epilepsy. Review of PSG studies in 40 children with epilepsy who underwent a sleep study for various sleep complaints showed that 40% had SDB (Kaleyias et al., 2008). Children with poor control of seizures had higher body mass index, lower sleep efficiency, and higher arousal index in comparison with children with good seizure control or children free of seizures (Kaleyias et al., 2008). Additionally, children with epilepsy and OSA had longer sleep latency and higher arousal index in comparison with children with OSA without epilepsy (Kaleyias et al., 2008).

A clinical feature likely predisposing children with epilepsy to SDB includes obesity and higher body mass index (Kaleyias et al., 2008; Kheirandish-Gozal and Gozal, 2008). High body mass index is a well-known risk factor for OSA in the general pediatric and adult population, and we have observed that children with epilepsy and OSA may have even higher body mass index than children with OSA only (Kaleyias et al., 2008). Higher rates of daytime sleepiness are seen in epilepsy patients with OSA in comparison with patients with OSA only (Malow et al., 2000b; Manni et al., 2003), indicating that epilepsy patients may have an even higher impact of sleep disturbance on their quality of life. A recent study including 26 children younger than 18 years concluded that OSA per se is an independent risk factor for cognitive disability in epilepsy, supporting the emerging notion that OSA may affect the quality of life of children with epilepsy, even when seizures are under control (Piperidou et al., 2008).

Many reports show that treatment of OSA by tonsillectomy and adenoidectomy or use nasal continuous positive airway pressure (CPAP) has resulted in better control of the seizures secondary to improved sleep fragmentation (Devinsky et al., 1994; Hollinger et al., 2006; Malow et al., 2003). In contrast, CPAP use has been responsible for precipitating parasomnias secondary to an SWS rebound. A recent article also showed that use of CPAP in an otherwise normal child resulted in activating a new onset of frontal lobe seizures, and the authors postulate mechanisms to explain the same (Miano et al., 2008).

Epilepsy may affect the regulation of respiration during sleep. Foldvary-Schaefer et al. (2008) 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.

Central Sleep Apnea

Central sleep apnea (CSA) has also been associated with seizures. CSA may trigger a seizure through the hypoxia caused by the central apnea itself that can reduce the seizure threshold (Blum et al., 2000). Conversely, it has been speculated that seizures may trigger a CSA (Tezer et al., 2009), or CSA may be an event at the end of the seizure (O’Regan and Brown, 2005; Trott and Bliwise, 2009). CSA is often seen accompanying diaphragmatic and glottic spasms during generalized tonic seizures. Central apneas can also occur with spread of focal seizures from mesial temporal and frontal lobes spreading to brainstem respiratory centers. A recent article showed good correlation of the central apneas with seizure spread from one temporal lobe to the opposite side, thus implying that bilateral input from the cortex may be necessary on the brainstem respiratory centers to induce CSA (Seyal and Bateman, 2009).

During seizures, patients often develop tachypnea, but bradypnea and hypventilation along with hypoxemia can also occur (Moseley et al., 2010). In a pediatric study involving 49 children and a total of 225 seizures, ictal hypoxemia was observed in 48.9% of children and 26.8% of seizures (Tezer et al., 2009). Ictal hypoxemia was more likely to occur during generalized seizures, and for partial complex seizures, there was an association between ictal hypoxemia and prolonged seizures (Tezer et al., 2009). In addition, during seizures there can be bradycardia/tachycardia and arrthymias, which can further complicate the breathing abnormalities. It is possible that such mechanisms during epileptic activity may contribute to central respiratory arrest and possible explanations for sudden unexplained death in epilepsy, especially if the child is in the prone position during the seizure (Asadi-Pooya and Sperling, 2009; Nashef and Rylin, 2009).

Effect of Epilepsy Therapies on Sleep Physiology

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is an approved therapy for the treatment of epilepsy in patients older than 12 years (Vonck et al., 2009). It works by inducing a constant electrical stimulation of the vagus nerve, transmitted retrograde in to the brainstem and the thalamus, thus reducing seizure frequency and intensity (Vonck et al., 2009). VNS has been shown to affect respiration during sleep and has been shown to also worsen preexisting OSA (Ebben et al., 2008; Malow et al., 2000a). VNS may also interfere with effective CPAP titration, suggesting that PSG and CPAP titration in patients with OSA should be conducted before VNS implantation (Ebben et al., 2008). A retrospective study on 26 children with epilepsy and VNS found new-onset OSA in four patients (15%) after placement of VNS, indicating that the VNS use may contribute to the development of OSA in predisposed children (Khurana et al., 2007).

Medications

Medications can contribute directly to the integrity of the upper airways and induce OSA. In particular, muscle-tone-reducing medications, including benzodiazapines such as lorazepan, clonazepam, and diazepam, can reduce muscle tone in the upper airway and cause its collapsibility during periods of muscle hyptonia (Chan et al., 2004). Valproic acid may induce obesity with resultant predisposition to OSA (Abaci et al., 2009).

Ketogenic Diet

Ketogenic diet is a high-fat, low-carbohydrate diet used for medically intractable epilepsy. Ketogenic diet decreases sleep time but improves sleep quality in children with therapy-resistant epilepsy (Hallbrook et al., 2007). The improvement in sleep quality, with increased REM sleep, seems to contribute to the improvement in quality of life. Indirectly, the reduction of IEDs and seizures on ketogenic diet may also contribute to improved sleep, reduced daytime sleepiness, and improved quality of life.

ASSESSMENT OF NOCTURNAL EVENTS

History

In general, it should be possible to accurately recognize most nonepileptic events from epileptic events during sleep on the basis of the clinical history. Children and parents should be asked about timing, duration, associated triggers, and a detailed description of the events. However, these events are not always witnessed and therefore pivotal elements of the history are often missing. In this setting, parents could provide home video recording of the spells, thus supplying invaluable additional information.
Routine EEG, Ambulatory EEG, and Inpatient Video-EEG

Routine EEGs have limited use in the differentiation between epileptic and nonepileptic events, although they may screen effectively for interictal epileptiform abnormalities, especially in the setting of idiopathic generalized epilepsy. More prolonged studies, such as 24-hour ambulatory studies, provide additional information for recurrent spell characterization, but it may be difficult to complete and accurately interpret in small children. Long-term video-EEG monitoring remains the gold standard for the characterization of these nocturnal events.

Video-PSG With Extended EEG Montage

Recognizing epileptic events during PSG can be difficult, particularly when using standard, limited EEG montages. An increasing number of sleep laboratories have PSG equipment that allows for the recording of 18 channels of EEG without compromising the ability to identify aperiodic, periodic limb movements, hypercapnia, and desaturations (Foldvary et al., 2000; Foldvary-Schaefer and Grigg-Damberger, 2009; Calabberti et al., 2009).

Few studies have shown that abbreviated EEG montages (4, 7, and 8 channels) are not adequate for the differentiation of seizures versus nonepileptic events during PSG (Foldvary-Schaefer et al., 2006). Although seizures localized to the temporal and parieto-occipital regions may be correctly detected and localized with abbreviated montages, frontal lobe seizures are more likely to be missed and only 18 channels EEG seem to allow the correct identification of these events (Foldvary-Schaefer et al., 2006).

In summary, these are the tools, and investigations that the physician may use to differentiate nocturnal epileptic/nonepileptic events are as follows:

1. Detailed history with description of events
2. Home videos by family members
3. Routine/sleep-deprived EEG
4. Ambulatory EEG (24–48-hour study)
5. Routine EEG
6. Video-PSGs with extended EEG montage

We recommend that inpatient long-term video-EEG monitoring may be used in differentiating sleep-related seizures from nonepileptic events. However, when a primary sleep disorder such as OSA, CSA, or periodic limb movements of sleep is possible on history, video-PSG with extended EEG montage should be performed. In differentiating parasomnias from FLE and RBD, video-PSG with extended EEG montage is extremely useful and highly recommended.

CONCLUSION

Several disorders present with paroxysmal motor activity out of sleep. Video-EEG and PSG technology has allowed the recognition of these events and their differentiation between epileptic and nonepileptic conditions. Most of the available studies in children consist of small retrospective observations, and many lack from availability of comprehensive video-EEG-PSG data. In addition, there is little understanding into the underlying biologic mechanisms involved in the pathogenesis of such phenomena. Epileptic and nonepileptic events may share common pathogenetic mechanisms. Additional insight may be provided from large prospective studies and animal data.

From a practical perspective, it should usually be possible for the pediatrician to accurately recognize most nonepileptic and epileptic disorders of sleep on the basis of the clinical history. However, some cases may present significant challenges. For instance, parasomnias, RBD, and nocturnal panic attacks may be easily confused with nocturnal frontal lobe seizures. Furthermore, and sleep disorders may coexist, making the distinction and the management of both diseases more challenging. This is particularly true with SDB presenting in children with epilepsy. Thus, routine EEG and PSG studies alone may be useful in some situations; recording of the events by using video-EEG-PSG is often required to make an accurate diagnosis.

REFERENCES


