# Sleep and Epilepsy

20

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## Abbreviations

| | |
|---|---|
| ADNFLE | Autosomal dominant nocturnal frontal lobe epilepsy |
| AED | Antiepileptic drugs |
| BRE | Benign Rolandic epilepsy |
| CPAP | Continuous positive airway pressure |
| CSWS | Continuous spike-wave during sleep |
| DRE | Drug-resistant epilepsy |
| EDS | Excessive daytime sleepiness |
| EEG | Electroencephalography |
| EMU | Epilepsy monitoring unit |
| GTC | Generalized tonic clonic |
| IED | Interictal epileptiform discharges |
| JME | Juvenile myoclonic epilepsy |
| LKS | Landau-Kleffner syndrome |
| NDD | Neurodevelopmental disabilities |
| NPO | Nil per os (nothing by mouth) |
| OSA | Obstructive sleep apnea |
| PLMD | Periodic limb movement disorder |
| PSG | Polysomnography |
| REM | Rapid eye movements |
| RLS | Restless leg syndrome |
| SE | Sleep efficiency |
| SL | Sleep latency |
| SUDEP | Sudden unexpected death in epilepsy |
| SWS | Slow-wave sleep |
| TST | Total sleep time |
| VNS | Vagus nerve stimulation |
| WASO | Wakefulness after sleep onset |

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## Introduction

Children with neurodevelopmental disabilities (NDD), regardless of the etiology, often have associated comorbidities. Among them, epilepsy is very common, and those children who have epilepsy frequently experience seizures during sleep. Seizures can occur both during daytime sleep and nocturnal sleep. It is known that children with epilepsy (even those without NDD) have significantly more sleep problems than their siblings or healthy controls [1]. It is essential for clinicians who work with children with NDD to understand how to evaluate and manage children who have epilepsy, particularly nocturnal epilepsy. Sleep can be disrupted either by the ictal event (seizure) and/or by the interictal (between seizures) abnormal brain activity. This disruption can result in daytime problems including (but not limited to) problems with memory, learning, behavior, attention, and daytime fatigue.

The incidence of epilepsy in children with NDD varies depending on the etiology of the child's intellectual delay as well as the severity. In many children, there is a relationship between those who have a lower intelligence having a higher incidence of seizures. An example of this correlation is reported in children with autism and epilepsy [2]. This correlation is understandable as, irrespective of the etiology of a child's NDD, increasing severity of cognitive delay is associated with more pathology in brain circuitry.

## Epilepsy

Seizures are common in childhood, affecting 4–16% of children before 16 years of age [3]. Epilepsy (which is characterized by recurrent seizures due to a genetically determined or acquired brain disorder) is also a common neurological condition in pediatric populations with an estimated lifetime prevalence of 1% [4]. Seizures result from electrical hypersynchronization of neuronal networks in the cerebral cortex. Seizures are divided into two types, generalized, where the ictus originates in all regions of the brain simultaneously,



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and focal/partial, where the ictus originates in one focal region of the brain and can potentially spread to other areas. In order to provide an understanding of the intricate relationship between sleep and epilepsy in children with NDD and to have an approach to the clinical management of children with this comorbidity, a brief review follows outlining common epilepsy definitions (Table 20.1).

## Seizures and Sleep

The connection between seizures and sleep has been recognized well before the era of evidence-based medicine, since the time of Hippocrates and Aristotle. In the modern era with advancements in the evaluation of children and adults with epilepsy, using neurophysiologic monitoring including polysomnography as well as continuous video EEG monitoring, much has been learned about the bidirectional relationship between sleep and epilepsy.

Sleep and epilepsy have two essential attributes in common. They are mediated by specific electrical oscillations of the brain networks and mediated by the same intrinsic cellular properties, sleep representing physiologic brain rhythms while seizures represent the evolution of normal oscillations into pathological patterns. Secondly, sleep and seizures share the same neuronal network, comprising the cerebral cortex, the thalamus and reticular thalamic nucleus, and the ascending modulatory systems from brainstem and forebrain. Thus it becomes obvious that the same mechanisms mediate both the different states of vigilance and the transformation of normal rhythms into paroxysmal epileptic activities. In addition, there are other factors influencing the bidirectional relationship between seizures and sleep such as the effects of antiepileptic medication (which can either stabilize sleep or contribute to changes in sleep architecture and daytime alertness) and the effect of other surgical or neuromodulatory therapies on sleep, as well as the effect of primary sleep disorders on seizures and epilepsy.

**Table 20.1** Common epilepsy definitions

| Term | Definition |
|---|---|
| Interictal epileptiform discharges (IED) | IED are brief, intermittent, and distinctive waves or complexes, present between seizures in the EEG recordings of people with epilepsy |
| Seizure | Seizures are paroxysmal clinical manifestations secondary to the presence of abnormal, excessive, synchronous electrical cellular activity in the brain |
| Epilepsy | Clinical condition characterized by a predisposition toward recurrent unprovoked seizures |
| Epilepsy syndrome | An epilepsy syndrome is an association of various clinical and electrographical EEG features that are specific for a particular type of epilepsy. Such features include age of onset, types of seizures commonly seen, part of the brain involved, clinical course, genetic etiology |
| Drug-resistant epilepsy (DRE) | DRE is a type of epilepsy in which seizure freedom cannot be achieved after two well-tolerated, appropriately chosen antiepileptic drugs were taken for an appropriate period of time |

## Effect of Sleep on Seizures

### Stages of Sleep Have Different Effects on EEG and Seizures

The transition from wakefulness to slow-wave sleep (SWS) is a consequence of a blockade of afferent synaptic volleys at the thalamic level and a deprivation of the cerebral cortex of external signals. This blockade promotes rhythmic high-amplitude, slow-oscillatory activities in the corticothalamic networks that underlie the slow waves seen on the EEG during SWS. In contrast activated states such as wakefulness and REM sleep are characterized by a desynchronized, low-amplitude EEG reflecting neurons being closer to the firing threshold, ensuring in this way an accurate transmission of information and an increased responsiveness to stimuli. This is why during sleep, when the cortical states are characterized by highly synchronous activities, there is an increased propensity for the spreading of the interictal discharges and seizures, given that at the cellular level these types of activities can seamlessly develop from the cortical slow oscillations. However, during the awake state and REM sleep, which are both activated cortical states, neurons are steadily depolarized and are more resilient to the spread and expression of both interictal discharges and seizures.

In clinical practice it is very important to assess the propensity for seizure both during sleep and wake. This is why it is common to evaluate a child with epilepsy by obtaining an EEG during sleep. Gibbs and Gibbs, pioneers in the use of EEG for the diagnosis and treatment of epilepsy, were the first to demonstrate the activation of interictal discharges by sleep and recognize the value of sleep clinical EEG recordings in obtaining a diagnosis of epilepsy as well as localization of the ictal onset. They reported that interictal epileptiform discharges were observed in about 36% of awake EEGs, but this number increased to 82% during sleep [5]. This finding remains true today.

Non-REM sleep is a powerful activator of interictal discharges [6]. The IEDs may or may not be present during wakefulness, but they increase at sleep onset, attain their maximum incidence during SWS, and can even become continuous in certain patients, producing an electrographical pattern called continuous spike-wave during sleep (CSWS) or electrographic status epilepticus during sleep (ESES). During REM sleep they are rare and usually localized to the most epileptogenic areas. The field of an interictal discharge

typically enlarges as sleep deepens and is strictly localized during REM sleep in patients with focal epilepsy. The fact that REM sleep is highly resistant both to the expression of interictal epileptiform discharges and to their cortical spread is useful in determining the seizure onset zone in patients with medically refractory epilepsy undergoing evaluation for epilepsy surgery [7].

For patients with generalized epilepsy, sleep is a less important activator, but a similar pattern of the expression of interictal discharges can be seen in most idiopathic generalized epilepsies. During slow-wave sleep, generalized interictal epileptiform discharges typically become more disorganized, and sometimes spike-wave discharges are replaced by higher-amplitude lower-frequency polyspikes. The findings seen during REM sleep are similar with the awake findings and are characteristic for the particular type of epilepsy [8].

### Sleep Deprivation Provokes Seizures

Sleep deprivation is recognized as a provoking factor for seizures, and it is used in clinical practice to increase the likelihood of capturing EEG abnormalities in patients with suspected epilepsy. Whether the activation of the interictal epileptiform discharges is produced by the sleep deprivation per se or is the effect on an increased time spent during SWS, sleep after sleep deprivation remains a subject of debate. While most clinicians consider that the degree of activation of IEDs by sleep deprivation is similar with that produced by natural sleep captured during routine procedures, there are also evidences that sleep deprivation is a stronger activator than natural sleep [9].

### Sleep Disorders in Patients with Epilepsy

Sleep disorders that are common in patients with epilepsy can contribute to poor seizure control due to inadequate quantity and/or sleep disruption. Sleep disruption and consequent increase in seizures can have many deleterious effects including problems with memory, learning, attention, behavior, and increased daytime fatigue. It is well recognized that sleep is important for learning and cognition, as has been studied in children with epilepsy [10, 11]. The clinician must be cognizant of the evaluation for any type of sleep disorders (e.g., insomnia, circadian rhythm disorder, sleep apnea, parasomnias as outlined in this textbook) when evaluating a child with epilepsy.

An example of a sleep disorder that should not be missed is obstructive sleep apnea (OSA). Obstructive sleep apnea treatment has been shown to improve seizure control in pediatric and adult patients with epilepsy and OSA [12–14]. In a retrospective review of 27 children with epilepsy and OSA, 10 subjects became seizure-free, and 3 had a significant reduction in seizures after surgical treatment (tonsillectomy and adenoidectomy). In a second smaller retrospective case series of nine children with NDD who also had OSA and epilepsy, seizure frequency was reduced in five of the nine children in the first year after treatment for OSA without any changes in AED treatment [15].

In a referred sample of adults with epilepsy, one third were found to have OSA [16]. The factors that may contribute to this high incidence are the weight gain seen with the use of specific antiepileptic drugs in parallel with a relatively decreased level of physical exercise. In addition, some AEDs may act as depressants of the central nervous system and may decrease the airway tone (especially barbiturates and benzodiazepines). The fragmentation of sleep and the sleep deprivation seen in patients with OSA lead to more frequent seizures, and conversely treating OSA can lead to better seizure control and even a decrease in the frequency of the interictal epileptiform discharges [12, 13, 17].

Adult patients with OSA have different treatment strategies and have been studied more thoroughly. In an adult cohort, the treatment of OSA with continuous positive airway pressure (CPAP) in patients with focal epilepsy not only normalized the apnea-hypopnea index but also produced a marked reduction in spike rate [17], thus supporting the hypothesis that OSA may increase the excitability of the cortical networks.

## Effect of Seizures on Sleep

### Seizures Alter Sleep Architecture, Leading to Hypersomnia, Sleep Fragmentation, and Arousals from Sleep

The normal sleep architecture and its continuity are essential for the normal daytime functioning of the individual, memory consolidation, and attention. These processes are affected when sleep architecture is disrupted. It is easier to study adult patients in a sleep laboratory as there are better defined normal values to which to compare the data. Adult patients with epilepsy experience a variety of alterations of the normal sleep architecture such as increased wake after sleep onset, increased number of arousals, decreased duration of REM sleep, and prolonged REM sleep latency [18, reviewed in 19].

There are several studies documenting the adverse effects of epilepsy on sleep patterns in children. In one study of 105 children with epilepsy (66% with developmental delay and 23% with autism), there were a number of changes in sleep patterns reported and sleep behavior when compared to controls. These changes included increased rates of both parent-child room sharing and co-sleeping as well as higher rates reported by parent questionnaire of parasomnias, night waking, shorter sleep duration, increased daytime sleepiness, and increase in sleep onset delay and in bedtime resistance [20]. These results highlight the importance in balancing parents' desire to co-sleep with their child who has nocturnal seizures with establishing good sleep practices (which is outlined in Chap. 28).

Children with NDD and epilepsy have a greater incidence of sleep problems and reduced sleep efficiency compared to children without epilepsy. In several studies, it is reported that there are some factors related to the epilepsy accounting for this association (e.g., nocturnal seizures, DRE, generalized seizures, and certain epilepsy syndromes) as well as comorbid factors (e.g., presence of developmental delay), increased anxiety related to sleep, and an increased incidence of behavior problems [1, 19, 21–23].

Many children with epilepsy complain about poor sleep quality and daytime sleepiness. While most of the time these are attributed to the secondary effects of the AED, a particular attention should be directed to children with mild seizures, on AED monotherapy, with normal AED serum levels, and with well-controlled seizures given that they may represent a primary sleep disorder [24]. These changes can impact children with NDD more than normal individuals given the preexisting burden of the disease on their daily functioning. Indeed, many children with NDD already have daytime problems with attention and memory, and they can be exacerbated not just by nocturnal seizures but also by an increased incidence of interictal discharges.

## Approach to the Evaluation of Epilepsy in Children

There may be many influences affecting sleep in children with NDD and epilepsy as discussed above and outlined in Fig. 20.3.

**Case Vignette #1**

A 6-year-old boy with developmental delay and autism presents with a 6-month history of regression. A previous routine EEG captured only wakefulness and was significant for the presence of IEDs (Fig. 20.1). Interictal abnormalities are seen in a large proportion of children with autism. The history of autistic regression prompted an overnight sleep EEG that demonstrated a very pronounced activation of the IEDs by sleep and the presence of continuous spike-wave during sleep (CSWS) (Fig. 20.2). This pattern resolved in the follow-up EEG after he was placed on medication, and this was associated with a significant improvement in his developmental skills.

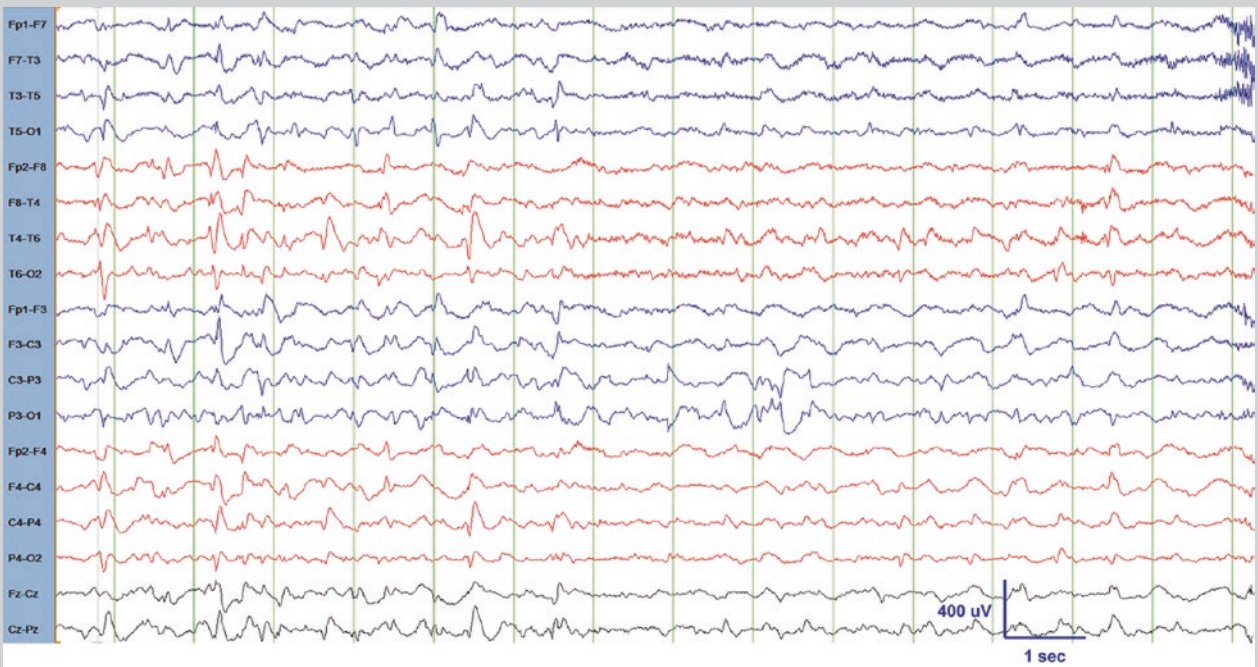


**Fig. 20.1** Awake EEG in a 6-year-old boy with developmental delay and autism (15 s, 21 channels, anteroposterior bipolar montage)

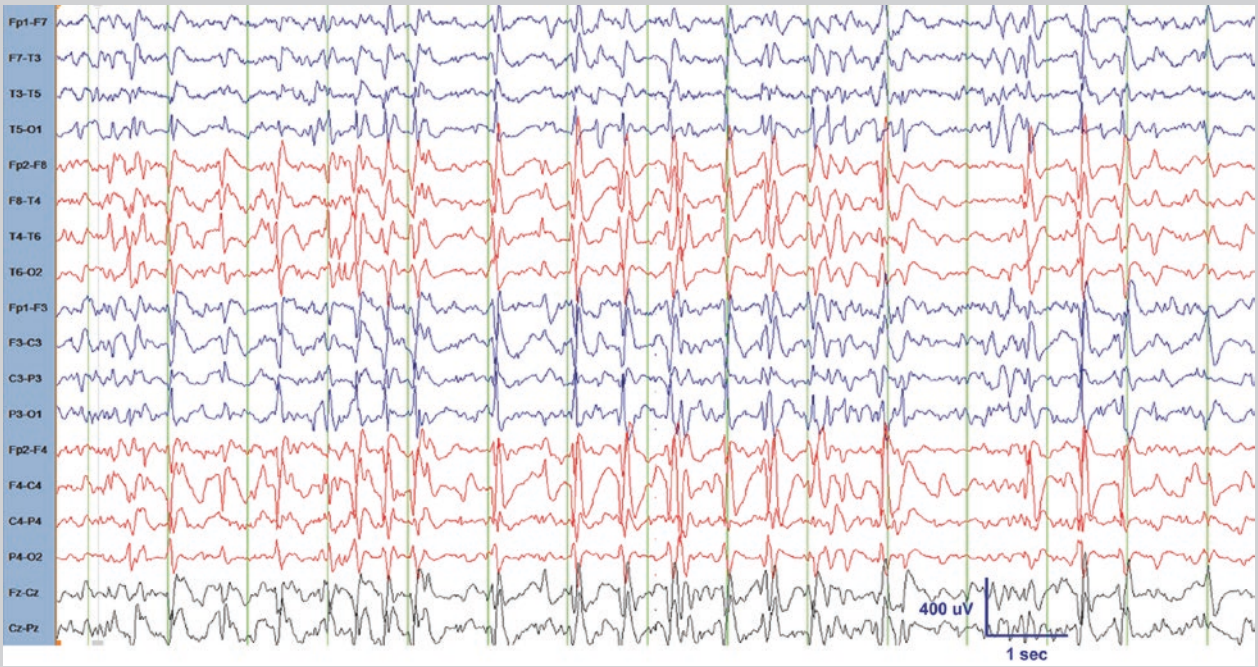


**Fig. 20.2** Continuous spike-wave during sleep captured during a sleep recording in the same patient, responsible for his regression (14 s, 21 channels, anteroposterior bipolar montage)

*Comment*

It is important for the clinician involved in the care of children with NDD, epilepsy, and sleep pathology to be aware of all these reciprocal interactions between seizures, sleep architecture, sleep deprivation, and possibility of sleep-activated interictal discharges. Although commonly children with this pattern will have seizures, other symptoms may include autistic behavior, regression, auditory agnosia, and/or deterioration in school performance. Many clinicians consider the terms CSWS and ESES interchangeably. CSWS/ESES is an epileptic encephalopathy with >85% spike-wave index.

## Epilepsy Syndromes with Seizures Related to Sleep

Certain epilepsy syndromes have a specific pattern of seizures in relation with sleep. These are outlined in Table 20.2.

## Evaluation of Children with Nocturnal Seizures

A detailed review of the evaluation of a child with NDD and possible nocturnal seizures is beyond the scope of this chapter. A careful clinical history and physical examination is required, followed by neuroimaging (usually a MRI), and EEG that captures both wake and sleep. In some cases, an overnight EEG and/or polysomnographic evaluation are also indicated.

There are a variety of neurophysiologic evaluations that can be used to diagnose seizures from other episodic non-ictal behaviors (Table 20.3). It is also important to differentiate localization related (focal) seizures from generalized seizures. These tests may include a daytime routine EEG (usually under 1 h) with sleep captured, an overnight video EEG recording, or an overnight polysomnography recording. In some clinical settings, the PSG includes either an expanded EEG montage or a full EEG recording. It is important for the clinician to understand the advantages and disadvantages of these evaluations in order to make informed decisions as to which evaluation is indicated.

## Practical Tips to Obtain EEG and PSGs in Children with NDD

### Sleep Deprivation

Often it is useful to obtain sleep during a daytime EEG recording to evaluate interictal discharges. This can be done

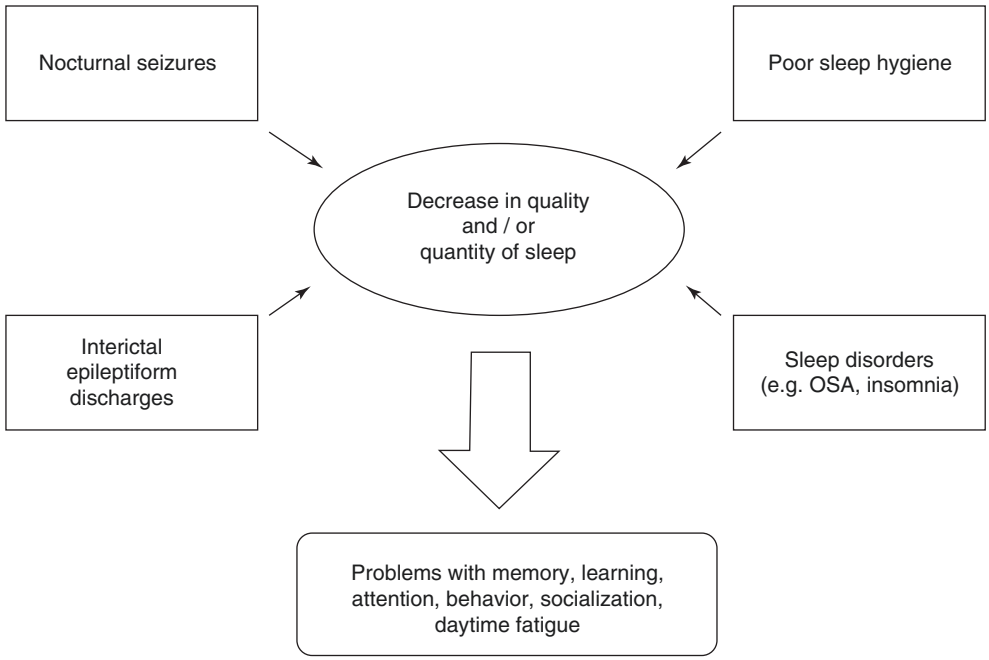


**Fig. 20.3** Factors influencing sleep in children with NDD and epilepsy

**Table 20.2** Epilepsy syndromes with seizures related to sleep

| | |
|---|---|
| Infantile spasms | Infantile spasms are a developmental epilepsy syndrome with onset between 3 and 18 months of age, characterized by an abnormal, chaotic, EEG background (hypsarrythmia), seizures consisting of flexor-extensor spasms of the body, and associated developmental delays. Hypsarrhythmia pattern may be present exclusively during sleep. The clinical spasms occur in clusters usually on awakening |
| Epilepsy with generalized toni clonic (GTC) seizures on awakening | Generalized epilepsy characterized by onset of generalized convulsive seizures between the ages of 5 and 40 years (peak 11–23 years). Seizures may be frequent and occur usually in the morning 1–2 h after awakening. Sleep deprivation, fatigue, and alcohol lower threshold for seizures |
| Juvenile myoclonic epilepsy (JME) | JME is characterized by myoclonic, absence, and GTC seizures that occur in the morning. Myoclonus is observed upon awakening and may evolve into generalized seizures. EEG is dominated by generalized, high-amplitude polyspike-wave discharges, frequently precipitated by photic stimulation |
| Benign occipital lobe epilepsy | The early onset benign occipital lobe epilepsy, also known as Panayiotopoulos syndrome, is characterized by prolonged periods of autonomic instability and generalized or hemiconvulsive seizures during sleep |
| Benign Rolandic epilepsy (BRE) | BRE, also termed benign epilepsy with centro-temporal spikes, is the most common focal epilepsy syndrome in children. Onset is between 3 and 13 years of age, and remission occurs in adolescence. Two thirds of children have seizures exclusively from sleep. On EEG, central and temporal lobe spikes are seen, which may be independent and bilateral with a horizontal dipole, prominently activated by sleep |
| Landau-Kleffner syndrome (LKS) | LKS is an acquired epileptic aphasia with language regression or auditory agnosia secondary to the presence of epileptiform activity in the temporal lobes. Onset is usually between 3 and 9 years of age. Motor seizures are rare, but epileptic abnormalities are present over the anterior temporal lobe and are enhanced by sleep. Frequently, a CSWS pattern is present during sleep |
| Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) | ADNFLE is an autosomal dominant epilepsy, produced by a mutation in the genes coding for the subunits of the nicotinic acetylcholine receptor (CHRNA4 or CHRNB2). Onset is in adolescence or young adulthood. The clinical manifestations include sudden awakenings with dystonic or dyskinetic movements, complex behaviors, and sleep-related violent behaviors. EEG findings include ictal epileptiform abnormalities predominantly over frontal areas in one third of patients or rhythmic slow-wave activity over anterior cortical areas in another half of the patients. Non-REM parasomnias have a high incidence, affecting about one third of the patients with ADNFLE |

**Table 20.3** Investigations used in the evaluation of child with nocturnal seizures

| Investigation | Advantages | Disadvantages |
|---|---|---|
| Routine awake EEG without sedation | Fast, without much disruption in child and family routine | May not record sleep or sleep-activated interictal discharges |
| Routine daytime EEG with sedation | Will capture sleep in daytime test and more likely to record interictal discharges | Child will require a period of NPO prior to evaluation and will require time to recover from the sedation |
| Sleep-deprived EEG | May not need sedation, or (in authors experience – unpublished) may be able to acquire sleep with combination of sleep deprivation and oral melatonin | May be able to capture sleep (avoid sedation) with sleep deprivation + melatonin only and, therefore, will not require as long to recover from test |
| Overnight video EEG | Will record all stages of sleep including N3. If seizures occur frequently may record event | Disruption of routine for child and family |
| Prolonged video EEG evaluation in epilepsy monitoring unit (EMU) | Diagnosis of seizure – if event occurs frequently but not every night, will increase chances of capturing event | Significant disruption to family |
| | | Not able to evaluate for sleep disorders as listed below in PSG |
| Ambulatory EEG | Can provide continuous EEG that is not disruptive to family in the home setting | Does not have video, so unable to diagnose or characterize seizures |
| Overnight polysomnography | Evaluate sleep architecture and rule out sleep problems such as OSA, non-REM arousal disorder, PLMD | Not as useful to evaluate for IEDs or seizures as EEG montage is limited |
| Home monitoring of sleep | Systems available to evaluate oxygen saturation | No system currently available that can evaluate sleep disorder |
| Actigraphy | Can evaluate sleep vs. wake | Technology currently not able to evaluate seizures or sleep architecture |

TIP: In addition to the above, having the parent record an event suspicious for a seizure or parasomnia on a cell phone or video camera can be very helpful in the evaluation of a child with potential epilepsy.

**Case Vignette #2**

A 3-year-old girl with Rett syndrome and no history of clinical seizures was referred for an overnight polysomnogram (PSG) to the sleep laboratory to rule out sleep apnea. The findings included borderline obstructive sleep apnea, mild central sleep apnea, and sleep fragmentation, as well as slow spike-and-waves throughout sleep. Following the PSG, to further evaluate her abnormal EEG activity, the child underwent an overnight EEG with a full montage to evaluate for either clinical or subclinical seizures and to further define her interictal discharges. The child did not have any seizures during the EEG recording, but this evaluation allowed for a better appreciation of her IEDs, which showed increased discharges during sleep that were multifocal. Snapshots of the PSG and EEG are shown below to illustrate the different information that is obtained from a PSG with an expanded EEG montage vs. a 21 channel EEG recording (Figs. 20.4, 20.5, and 20.6).

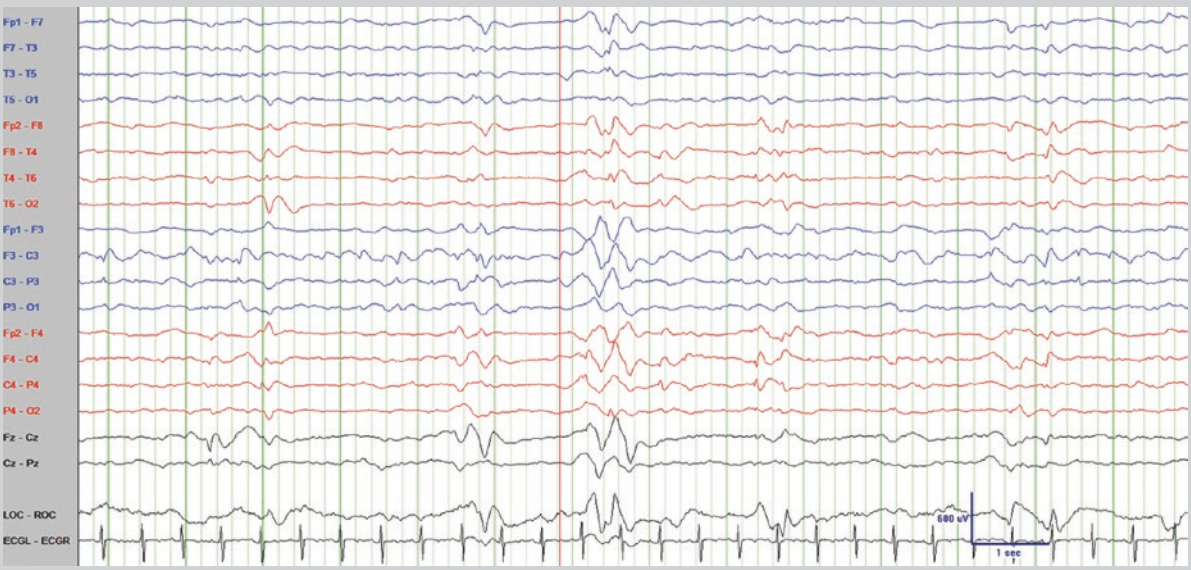


**Fig. 20.4** Epoch of wake on EEG with 21 channel EEG recording (14 s, 21 channels, anteroposterior bipolar montage)

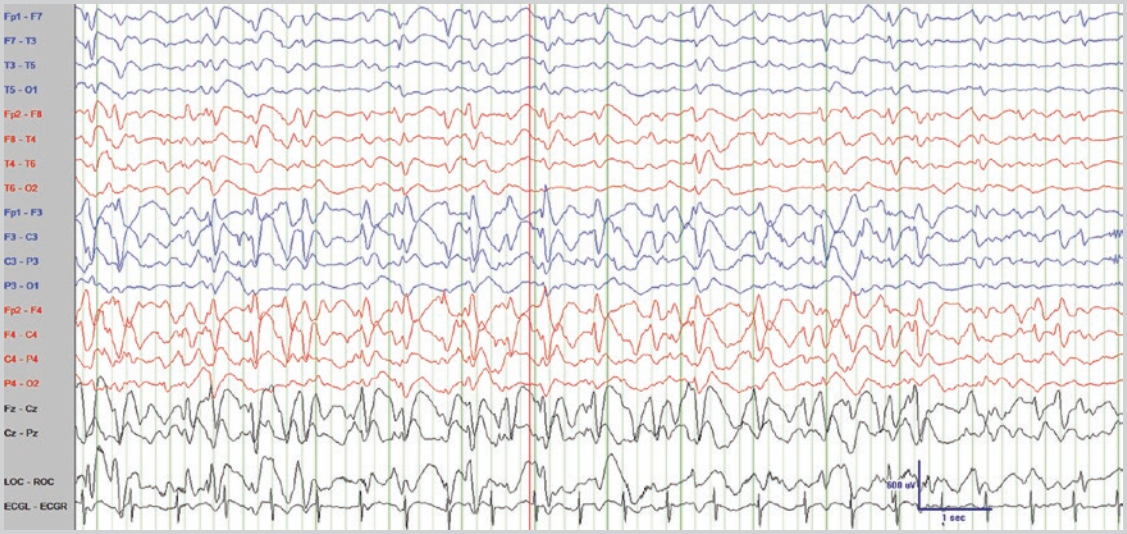


**Fig. 20.5** Epoch of sleep demonstrating activation of IEDs on EEG with 21 channel EEG recording (14 s 21 channels, anteroposterior bipolar montage)

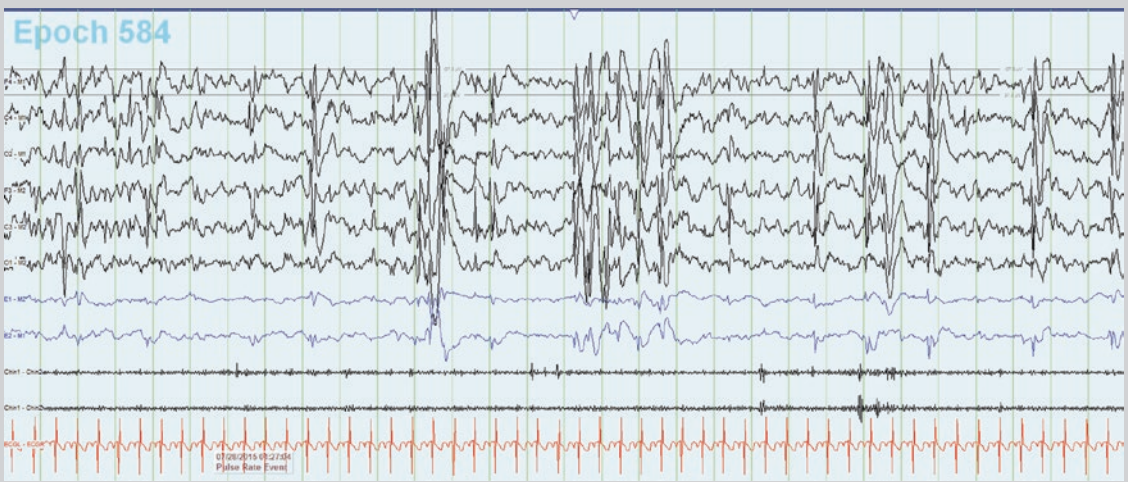


**Fig. 20.6** Epoch of PSG during N2 sleep demonstrating the presence of IEDs (14 s, six channels, referential montage)

*Comment*

Clinicians must be cognizant of the limitations of PSG in the evaluation of both interictal discharges and nocturnal seizures. In some laboratories, the PSG will be done with an expanded EEG/seizure montage but this will not include (in most) a 21 channel EEG recording. Although one will see abnormal spike-wave activity (as demonstrated in this example), it will not be possible to evaluate the localization or extent of the IEDs. In addition, due to movement artifact and limited EEG coverage during a PSG, the ictal features of a frontal lobe seizure may not be able to be appreciated. Therefore, it is often necessary to perform both evaluations: a PSG to evaluate for primary sleep disorders, and also an EEG or overnight EEG to evaluate for ictal and interictal activity.

by sleep depriving a child before the EEG. The method of sleep deprivation (e.g., number of hours) may vary from one neurophysiology laboratory to another. Sleep deprivation, combined with scheduling the EEG at the child's usual nap time, can be used and may avoid the need to use a sedative medication for the EEG.

### Use of Melatonin

There is limited evidence in the literature for the use of sleep-inducing agents, such as melatonin, to obtain sleep recordings during a daytime EEG [25–27]. In the authors' experience (not published), the combination of sleep deprivation with oral melatonin for children who are both typically developing as well as those with NDD can be helpful in obtaining sleep during a daytime EEG recording.

### Practical Technical Tips

The same tips as outlined in Chap. 3 on PSG are useful in the evaluation of a child with NDD for an EEG. For a further excellent practical summary of technical tips, see Paasch et al. [28].

## Treatment Options for Children with Epilepsy

There are several options in the treatment of children with epilepsy. Medical management is the first line. Children are generally started on a single antiepileptic drug chosen by the clinician as most appropriate for the seizure type with the highest efficacy and least side effects. If the first AED fails as monotherapy, then a second AED is added or substituted.

Epilepsy surgery is reserved for patients with DRE, who failed at least two properly chosen AEDs, well tolerated by the patient, and trialed for an appropriate period of time. Procedures used may include resective procedures (e.g., corticectomies, lobectomies), disconnection procedures (e.g., hemispherotomies, multiple subpial transections), and laser ablation. Many children with NDD and structural brain abnormalities benefit from these procedures, and the presence of a NDD is not a contraindication for surgery.

Children with DRE who are not candidates for surgery may benefit from the ketogenic diet and/or implantation of neuromodulating devices such as the vagus nerve stimulator (VNS).

**Case Vignette #3**

An 8-year-old girl who was diagnosed with autism at the age of 2 years is referred for consideration of epilepsy surgery. The girl is nonverbal but can communicate using signs and functions at the cognitive level of a 4-year-old. She has many stereotypies and significant socialization issues as well as anxiety. At the age of 5 years, she developed complex partial seizures which usually occur upon waking but can also occur during wake. Despite a trial of two AEDs, the child continued to have seizures. She underwent neuroimaging and was found to have a small left hippocampus with increased signal on FLAIR sequence (Fig. 20.7), most likely consistent with mesial temporal sclerosis. Next, the child underwent a video EEG which captured four seizures. All seizures consistently arose from the left temporal lobe. The child also underwent a neuropsychological evaluation, limited by her cooperation, anxiety, and cognitive challenges, which showed global delay in both verbal and visual memories. Following these evaluations, she underwent a left mesial temporal resection, and the pathologic diagnosis was subpial gliosis in the left temporal lobe and left hippocampal sclerosis. Following surgery, the seizures resolved without any new deficit in her memory or learning. She continues to have challenges related to her ASD, anxiety, and cognitive delay. The child remained on AEDs following surgery for 2 years, until the age of 10 years, at which time she was successfully weaned off her AEDs.

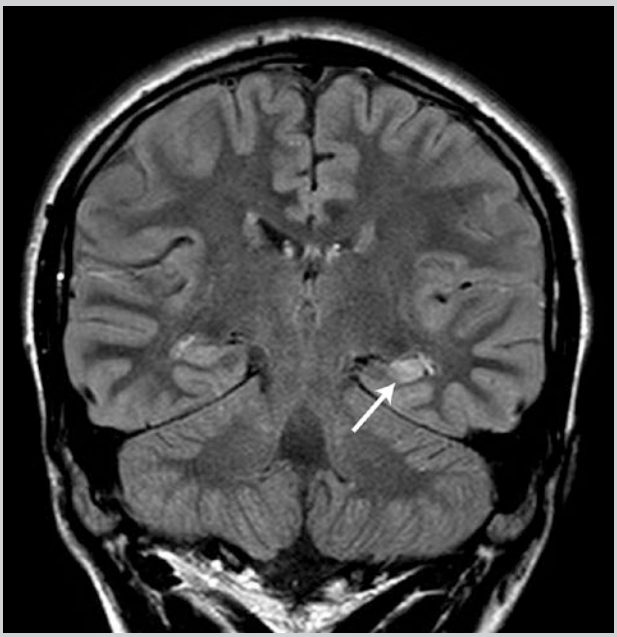

**Fig. 20.7** Coronal FLAIR MRI sequence demonstrating abnormal signal in left mesial temporal lobe and left hippocampus with associated volume loss. Arrow indicates increased signal on FLAIR sequence in left hippocampus

*Comment*

This case illustrates that when a child has medically refractory epilepsy, it is important to refer the child for consideration of surgical options to decrease or eliminate seizures. The presence of NDD (as evident in this child) should not preclude evaluation for epilepsy surgery.

## Antiepileptic Drug Treatment and Sleep

The goal of antiepileptic pharmacotherapy is to control seizures by achieving a prolonged seizure-free state. A clinician will choose the most appropriate medication after evaluation of the child's seizure type, epilepsy syndrome, and consideration of potential drug side effects. Other considerations in choosing an AED include the preference for monotherapy, choosing an AED with minor interference with sleep, administration of the minimal effective dose, and attention to the timing of drug administration [29, 30]. Considering all of these variables will be important to try to maximize good sleep and decrease daytime somnolence in children with epilepsy.

There are few studies evaluating the effect of AEDs on sleep architecture in children with epilepsy. It is also difficult to evaluate this association, as it is unknown if the sleep architecture is altered primarily by the AED or by underlying brain abnormality causing the child to have seizures. In one study [31], children with epilepsy were evaluated by polysomnography. Sleep architecture seemed to be influenced by the number of AEDs, with children having decreased REM sleep and decreased sleep efficiency if treated with two or three AEDs. Further research on the effect of AEDs on the sleep architecture of both children who are typically developing and those with comorbid neurologic/cognitive challenges is needed.

What has been shown in studies of adults with epilepsy is that AEDs may have differing effects on sleep, with some causing detrimental effects, and others stabilizing sleep [29]. It may be difficult to definitively determine these effects on people with epilepsy, as it is difficult to separate the effect on sleep from a drug itself vs. the effect on sleep from decreasing both ictal and interictal activities. Drowsiness is one of the most frequent side effects of AEDs [29, 30]. In some children this will be a transient effect, experienced with the introduction of the drug or titration of AEDs to higher doses.

Antiepileptic drugs have variable effects on sleep architecture, but most AEDs do affect sleep architecture. In a recent evidence-based systematic review on the effects of epilepsy treatments on sleep, gabapentin, tiagabine, pregabalin, clobazam, and carbamazepine were found to reduce sleep latency and/or improve sleep efficiency [32]. Phenobarbital, valproic acid, and high-dose levetiracetam aggravated daytime sleepiness, whereas topiramate and zonisamide did not. Some of the known effects of AEDs on sleep are summarized in Table 20.4.

## Sleep After Epilepsy Surgery

The literature focusing on sleep architecture after epilepsy surgery is sparse. In one adult study that evaluated sleep before and after epilepsy surgery [33], no signifi-

**Table 20.4** AED effects on sleep

| | Awake/arousals | N1 | N2 | N3 | REM | SE/TST | SL | WASO |
|---|---|---|---|---|---|---|---|---|
| **PB** | – | | + | | – | | – | |
| **PHT** | | – | + | | – | – | – | |
| **VPA** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **CBZ** | – | 0 | 0 | + | – | + | – | |
| **ESM** | | + | | – | + | | | + |
| **BZD** | – | – | + | – | | | – | – |
| **VGB** | – | | | | | | | |
| **GBP** | – | – | | + | + | | | |
| **LTG** | | | | – | + | | | |
| **TPM** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **FBM** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **LEV** | | | + | | – | + | | – |
| **PGB** | – | – | – | + | – | + | | – |
| **ZNS** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **TGB** | | | | + | | + | | |

Data from Refs. [29, 30, 32]

*PB* phenobarbital, *PHT* phenytoin, *VPA* valproic acid, *CBZ* carbamazepine, *ESM* ethosuximide, *BZD* benzodiazepines (e.g., lorazepam, diazepam, clonazepam, clobazam), *VGB* vigabatrin, *GBP* gabapentin, *LTG* lamotrigine, *TPM* topiramate, *FBM* felbamate, *LEV* levetiracetam, *PGB* pregabalin, *ZNS* zonisamide, *TGB* tiagabine, *SE* sleep efficiency, *TST* total sleep time, *SL* sleep latency, *WASO* wakefulness after sleep onset, + increase, – decrease, 0 no effect found, empty cells – no data

cant changes were seen. However, in a group of patients with postoperative Engel classes I and II, increased total sleep time (TST) and reduced arousals were seen, while no changes were present in the subjects who continued to have frequent seizures [34]. Therefore, we can speculate that it is probable that after successful epilepsy surgery, children's sleep would improve, as would daytime somnolence. However, this has not been directly demonstrated to date.

## Sleep in Children on Ketogenic Diet

The ketogenic diet is a high-fat, low-carbohydrate diet used in children and adults with DRE. It was shown that ketogenic diet improves sleep quality in children with DRE [35]. In a cohort of 18 children with refractory epilepsy, at the onset of the diet, there was a significant decrease in TST, mainly due to decreased N2, while REM sleep duration was increased. At 12-month follow-up, there was a further increase in the duration of REM sleep and a decrease of daytime sleep [35].

## Sleep in Patients with Vagus Nerve Stimulators

Vagus nerve stimulation is an adjunctive therapy usually reserved for patients with drug-resistant epilepsy who are not candidates for epilepsy surgery. VNS effects are produced by the application of current pulses to the vagus nerve, thus modulating CNS excitability. VNS alters sleep architecture, and the continuous stimulation is associated with increased awakenings and wake after sleep onset (WASO), increased N1 sleep stage, and decreased REM sleep [36, 37].

The VNS device is activated at preset intervals to deliver pulses for a certain duration of time. During these periods, there is a decrease in airflow and breathing effort. In a cohort of 16 adult patients with intractable epilepsy who underwent VNS implantation and had formal PSG before and after VNS placement, an apnea-hypopnea index (AHI) >5 was observed in five patients, only one of whom had preexisting sleep apnea [38]. Similar findings have been reported in children with epilepsy. The intensity of the stimulation is correlated with the severity of VNS-related respiratory events, and a reduction in the stimulation frequency can ameliorate these events.

## Evaluation for Sleep Disorders in Children with NDD

It is well known that any cause of sleep deprivation can trigger more seizures. Therefore, when a child with NDD has epilepsy, it is imperative to evaluate for the presence of other sleep disorders. All of the sleep disorders outlined elsewhere in this book may be present in a child with seizures. The most common are behavioral insomnia (outlined in Chap. 5 and elsewhere) or the presence of obstructive sleep apnea or parasomnias. Treating the underlying sleep disorder and improving the continuity and duration of sleep may decrease the frequency, duration, or intensity of the nocturnal seizures. Some case examples to illustrate these comorbidities follow.

## Sleep, Epilepsy, and OSA

**Case Vignette #4**

A 5-year-old boy is seen by his pediatrician for noisy breathing and snoring at night. The child was born at 32 weeks' gestation and developed periventricular leukomalacia which has resulted in spastic diplegic cerebral palsy, mild cognitive impairment, and attention deficit disorder. At the age of 2 years, he also began to have complex partial seizures during both wake and sleep. In addition, he continued to have frequent seizures despite several trials of AEDs. After evaluation (history and physical examination), the child was referred for an overnight polysomnograph which showed the presence of moderate obstructive sleep apnea. After referral to an otolaryngologist followed by a tonsillectomy and adenoidectomy (T&A), his parents reported resolution of his snoring and improvement in his sleep duration. He continued to have both wake and sleep seizures; however without any increase in AED dose or changes to his medications, the frequency of both wake and sleep seizures decreased by 50%.

*Comment*

As outlined in Chap. 6 on sleep-related breathing disorders, always take a history of signs of OSA, and consider PSG if there is clinical suspicion of OSA. Most children with NDD, even when there is severe intellectual impairment, can be evaluated in a sleep laboratory. However, if a child is unable to cooperate, and there is clinical suspicion of OSA, it is still worthwhile to refer for an otolaryngology consultation for consideration of T&A.

## Sleep, Epilepsy, and Parasomnias

**Case Vignette #5**

A 5-year-old child with fetal alcohol spectrum disorder, developmental delay, and seizures was referred as he had recently begun to wake several times per week (often within 60 min of falling asleep) with an inconsolable cry. When parents went to the child's room, they found that he was tachycardic, tachypneic, and diaphoretic. Parents were not able to determine if the episodes are seizures, as they did not resemble his typical semiology during a seizure. There were no abnormal rhythmic movements and no clear automatisms. After an episode, which lasts 5–15 min, he settled back to sleep and had no memory of the event in the morning. An overnight EEG that captured these episodes showed no electrographical correlate.

*Comment*

This case illustrates that children can have both slow-wave arousal parasomnias (as described above) and seizures. The clinician must be able to differentiate these two phenomena as the evaluation and management differ greatly.

### Parasomnias in Children with Epilepsy

Parasomnias (especially slow-wave arousal disorders) are commonly seen in children with epilepsy and seizures, especially frontal lobe epilepsy, and may be difficult to differentiate from each other. Adult patients with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) have a high incidence of arousal parasomnia (up to 30%), and 12% have REM behavioral disorder [39, reviewed in 40]. Parasomnias may be present in other focal epilepsies, but the incidence is low. The non-REM parasomnia (also called arousal or slow-wave parasomnia) events tend to be longer, have different patterns, and occur during the earlier part of the night, developing during stage N3 sleep (Table 20.5). Seizures tend to be shorter and highly stereotypic. They may occur multiple times throughout the night, from various stages of sleep [40, 41]. The following table outlines some clues in the clinical history and neurophysiologic evaluation to differentiate a child who is having non-REM arousal parasomnias from nocturnal frontal lobe seizures.

### Sleep, Epilepsy, and Insomnia

In children with epilepsy, sleep disturbances are mostly studied through parental questionnaires, and there are few if any objective studies available in the literature assessing the specific incidence of insomnia. In adults, insomnia is present in up to 55% of patients with epilepsy [42]. Incidence in children is estimated at approximately 11% based on the number of children with bedtime difficulties and families that report increased parent/child interaction during the night [43]. The presence of insomnia correlates with the number of AEDs, used, and both factors are predictors of poor quality of life [44].

**Table 20.5** Non-REM arousal parasomnias versus nocturnal frontal lobe seizures

| Feature | NREM arousal parasomnias | Nocturnal frontal lobe seizures |
|---|---|---|
| Age of onset | Usually <10 years | Variable: usually childhood or adolescence |
| Time of onset | Usually within first 2–3 h of sleep onset | Randomly, at any time of the night |
| Number of attacks/night | 1 or 2 | Variable, can be >3 |
| Duration (mean) | Seconds to 30 min | Generally short, often <2 min |
| Stereotypy | Absent | Present |
| Recall of event | Impaired unless child awakened during parasomnia by parent/caregiver | Can either be impaired (if secondarily generalized) or preserved |
| Post attack state | Will generally fall back to sleep quickly | May or may not fall back to sleep quickly |
| Sleep stage | Usually occurs from N3 | Usually occurs from N1 or N2, occasionally N3 |
| EEG during event | No IED or seizure activity | IED or seizure may or may not be present. May be obscured by movement artifact |

### Sleep, Epilepsy, and RLS/PLMD

There are few studies on the incidence of restless leg syndrome (RLS) and periodic limb movement disorder (PLMD) in children with epilepsy. In adults it is reported that 35% of adults with epilepsy may have RLS, and 15% may have PLMD [45]. In one study, 10% of children with epilepsy (out of 40 involved in the study) had periodic limb movements of sleep; however, further research is needed as this was a population referred to a sleep center because of various sleep complains [46]. Since PLMD may result in fragmented sleep and thus increased risk for seizures, consideration should be given to evaluation and treatment of children with possible PLMD/RLS.

### Sleep, Insomnia, and EDS

Excessive daytime sleepiness (EDS) is the most common sleep/wake complaint among people with epilepsy, typically attributed to the effects of AEDs and seizures. Several studies have found that one third to one half of the population with epilepsy reports EDS. EDS seems to be related more frequently to undiagnosed sleep disorders than to epilepsy-related factors, and although it affects the quality of life of children with epilepsy, it can be improved by treating comorbid primary sleep disorders [47].

## Sudden Unexpected Death in Epilepsy (SUDEP)

It is important to review sudden unexpected death in epilepsy (SUDEP) in a chapter on sleep and epilepsy in children with NDD as unfortunately, this is an unpredictable cause of fatality which when it occurs, is often associated with sleep in this population. SUDEP is a "sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy with or without evidence for a seizure and excluding documented status epilepticus in which postmortem examination does not reveal a toxicologic or anatomic cause for death" [48]. Children and adults with epilepsy have a 20-fold increased risk of sudden death compared to the general population. The incidence is as high as 9.3 per 1000 patient-years among patients with DRE evaluated for epilepsy surgery or VNS [49]. Refractory seizures, frequent generalized tonic-clonic seizures, and the presence of major neurologic impairments are considered to be its main risk factors in the pediatric population [40]. Respiratory abnormalities, such as central and obstructive apneas, hypoventilation, hypercapnia, and desaturation with acidosis, bradypnea, and tachypnea, and cardiac abnormalities, such as postictal changes in heart rate variability, ictal bradycardia, asystole, repolarization anomalies, and atrial fibrillation, have been proposed as putative mechanisms for SUDEP [40, 50]. In addition, cerebral shutdown seen as postictal EEG suppression may represent another mechanism of SUDEP. The evidence currently available for possible mechanisms for SUDEP and potential preventative mechanisms is outlined in a recent review by Massey and colleagues [51].

## What Is on the Horizon That May Help Children with NDD Who Have Sleep-Related Epilepsies?

There is ongoing research with the goal of developing new technologies that may be able to detect and abort seizures. At the current time, there is no device that is safe and effective and available for patients. Some families use service dogs trained to detect their child's seizures and alert an adult. At this time, there is no reliable device or other method (including service dogs) to reliably alert a parent when a child has a seizure during sleep.

## Conclusion

Epilepsy is a common comorbidity in children with NDD, and although seizures may occur both during wakefulness and sleep, they frequently occur during sleep. There is a well-established bidirectional relationship between sleep and epilepsy, with epilepsy and interictal discharges disrupting sleep and sleep disorders exacerbating seizures. There are also mimics of seizures that occur during sleep, most importantly slow-wave arousal parasomnias. It is important for clinicians to be aware of these associations and evaluate children with epilepsy for sleep disorders. The treatment of sleep disorders in this population can have profound effects by decreasing seizure frequency and improving sleep quality and quantity which will result in improved memory, learning, attention, and quality of life.

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