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Review Article

Sleep Disorders in Childhood Epileptic Disorders

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Abstract

Sleep disorders are common in children, especially in children with epileptic disorders. This article reviewed most recent publications supporting a reciprocal relationship between sleep disorders and childhood epileptic disorders as well as the underlying mechanisms involved in both disease processes, i.e. similar neuronal networks in the genesis of sleep and epileptic seizures. Evidence support that sleep disorders can aggravate Interictal Epileptiform Discharges (IEDs) and nocturnal seizures in children with epilepsy, leading to poor seizure control and increasing functional disturbance in patients with childhood epileptic disorders; On the other hand, childhood epileptic disorders and some antiepileptic medications and vagus nerve stimulator can change sleep quality and architecture of sleep, resulting in an increase in troubled sleep, which can lead to increased sleep disorders. Recognizing and effectively treating sleep disorders in patients with childhood epileptic disorders can improve seizure control and overall functioning and vice versa.

Introduction

Epilepsy is the most common neurological disorders in children [1]. It is characterized by recurrent unprovoked seizures. Seizures are transient brain dysfunction caused by excessive hyper synchronous discharge of a large group of neurons [2]. Epileptic seizures are used to distinguish provoked seizures which are caused by reversible insults such as fever, infection, hypoglycemia or medication. Epilepsy syndromes refer to a group of clinical characteristics that consistently occur together such as similar age of seizure onset, seizure types, EEG features, triggering factors, genetics, natural history, prognosis and responses to Antiepileptic Drugs (AEDs) [3]. Interictal Epileptiform Discharges (IEDs) are brief paroxysmal electrographic discharges usually seen between seizures in epileptic patients. Common IEDs are interictal spikes (<70 msec duration) and sharp waves epileptiform discharges (70-200 msec duration). It is commonly accepted that increasing frequency of IEDs are associated with increased risk of seizures in patients with epilepsy [4].

Childhood sleep disorders are conditions that cause insufficient sleep or excessive sleepiness [5]. Sleep problems in children can be categorized as either behavioral or medical. Behavioral sleep problems are often due to poor sleep hygiene caused by a lack of routine, poor sleep environment and insufficient sleep. Medical sleep conditions are often result from an endogenous disturbance in sleep-wake generating mechanisms and complicated by behavioral conditioning. Common childhood sleep disorders are insomnia, Obstructive Sleep Apnea (OSA), central sleep apnea, hypoventilation, circadian rhythm disorders, narcolepsy, parasomnias, restless legs syndrome and periodic limb movement disorder. Childhood sleep disorders are now recognized as one of the common causes leading to developmental regression, behavior disturbance, learning disability, memory deficits and poor school performance [6].

The relationship between sleep and epilepsy is complex and reciprocal [7,8]. Sleep has strong influence on IEDs and on epileptic seizures [9] and epilepsy significantly affects sleep quality, sleep architecture and restorative functions of sleep [10]. Sleep disorders are extremely common in patients with epilepsy [11]. The available research indicates that children with epilepsy have a higher frequency of sleep problems than both their healthy siblings and healthy control subjects [12]. Jain et al [13] studied the incidence of sleep disorders in 108 subjects with epilepsy including 84 patients with partial seizures, 16 patients with generalized epilepsy, and 8patients with unclassified epilepsy. Among the patients with partial seizures, 40% had obstructive sleep apnea, 6% had hypoventilation, 7% had central sleep apnea, 12% had insomnia, 5% had periodic limb movement disorder, 14% had primary snoring, and 6% had any other sleep disorder and only 10%patient had no sleep disorder identified. Among patients with generalized epilepsy, 38%had obstructive sleep apnea, 6% had hypoventilation, 6% had central sleep apnea, 12% had had insomnia, 6% had periodic limb movement disorder, 19% had primary snoring, and 13% did not carry a sleep disorder diagnosis at the end of the evaluation. This result shows that sleep disorders are common in patients with both generalized and partial epileptic disorders.

Common Sleep Disorders in Childhood Epileptic Disorders

Sleep problems are one of the most common comorbidities in epilepsy [14]. Becker et al [15] studied the relationship between sleep disturbance and daytime behavior in children with epilepsy. Parent-rating questionnaires and child symptom self-report measures were employed to evaluate daytime behavior in 30 children with epilepsy and sleep-disordered symptoms. Overnight polysomnography was used to assess for nocturnal sleep problems such as obstructive sleep apnea, nocturnal seizures, periodic leg movements, and sleep fragmentation. Their results showed that 80% of children with epilepsy exhibited sleep disruption because of either clinically significant obstructive apnea syndrome, disturbance of sleep architecture, or sleep fragmentation. This study indicates that daytime behavior problems encountered in children with epilepsy may be attributed to specific disruptions in sleep regulation.

Obstructive Sleep Apnea (OSA)

Obstructive sleep apnea is the most prevalent sleep disorders in patients with both generalized epilepsy and partial seizures [13]. Jain et al [16] conducted a prospective pilot study in children with epilepsy to identify the prevalence of OSA and its relationship to the use of Antiepileptic Drugs (AEDs) and epilepsy types. They used Michigan Pediatric Sleep Questionnaire (PSQ) in children with epilepsy. Patients were classified by seizures frequency as mild (0-1 seizure/month) or severe, refractory epilepsy (> 1 seizures/month). Their result showed that of 84 children, 52 were classified as mild and 32 as severe. Prevalence of OSA was significantly higher in the severe (43.8%) *vs* the mild group (30.7%, P < 0.05). Children on >1 AED had significantly higher prevalence of OSA (45.8%) than children on ≤1 AED (30.6%, P < 0.05). There was no significant correlation between the prevalence of OSA and seizure types. They concluded that OSA is more prevalent in refractory epilepsy and in children who are on multiple AEDs.

A more recent study by Gogou et al [17] showed that the prevalence of OSA was significantly higher in the epilepsy patients (35% *vs* 7.4%, p<0.01). Moreover, the odds ratio of an obstructive apnea index ≥1 in the epilepsy patients was 10.6 (95% Confidence Intervals: 3.08-37.08) in comparison to the control group. The mean value of the obstructive apnea-hypopnea index was significantly higher in children with epilepsy compared to healthy children (2.46±1.22 *vs* 1.21±0.83, p=0.027). The authors concluded that children with epilepsy seem to present more prominent sleep breathing instability in comparison to healthy children, which mainly includes a predisposition to obstructive respiratory events.

Gogou et al [18] in 2015 reviewed studies regarding the prevalence of sleep apneas in children with epilepsy. They used PubMed as the medical database source, and articles were selected and classified according to their originality, level of evidence, and relevance to the broad scope of the review. Their data showed that children with epilepsy have a higher prevalence of obstructive apnea in comparison to healthy children, but this prevalence varies widely depending on the methodology of each study. Major risk factors for sleep apneas in childhood epilepsy include poor seizure control and on multiple antiepileptic medications [18].

Urquhart et al [19] studied obstructive sleep apnea symptoms among 33 children with epilepsy (21 males, 12 females), along with 42 controls (20 males, 22 females). They found that 55% children with epilepsy scored 0.33 or higher on the sleep-related breathing disorder questionnaire compared with 7% in the comparison group (p<0.001). Within the children with epilepsy cohort, both sleep-related breathing disorder questionnaire and Epworth sleepiness scale appeared higher in those taking antiepileptic drugs; although these was higher than in the comparison group. Their study suggests higher rates of symptoms of obstructive sleep apnea and excessive daytime sleepiness in children with epilepsy compared with typically developing children. AEDs may be a confounding factor, but do not alone account for the associations seen.

Sleep-Disordered Breathing (SDB)

Klobucnikova et al [20] conducted a study to evaluate the relationship between SDB and daytime sleepiness in patients with epilepsy. They enrolled 40 patients with epilepsy and all of them underwent overnight PSG. EDS was assessed by Epworth Sleepiness Scale (ESS). Their result showed that SDB was present in 25 (63%) patients and EDS in 16 patients (40%). They concluded that SDB has negative influence on quality of sleep and daytime virility in patients with epilepsy. Sleep fragmentation with the reduction of the REM sleep seems to be the most important mechanism leading to EDS. Regarding the cause of increased SBD in patients with epilepsy, it is possible that increasing IEDs during sleep, nocturnal seizures or hypoxic encephalopathy can change sleep architecture with increase of light sleep and reduction of REM sleep, which may lead to central apneas and SDB.

Insomnia

In children with epilepsy, insomnia was identified in 11% [13]. Insomnia and poor sleep quality were predictors of poor quality of life and poor seizure control. Khatami et al [21] reported in 100 patients with epilepsy, sleep-onset insomnia was reported in 34% and maintenance insomnia in 52%. Sleep onset and sleep maintenance insomnia were significantly higher in epilepsy patients (20%, 24%) than in healthy controls (6%, 12%). The effects of epilepsy severity including presence of nocturnal seizures, type of seizures, duration of epilepsy, type and number of AEDs, and presence of EEG abnormalities on insomnia were investigated. Accordingly, the presence of nocturnal seizures was significantly higher (47%) in epilepsy patients with insomnia than in epilepsy patients without insomnia (31%). Moreover, history of a 2-year seizure free period was more common in patients without insomnia (26%).

Excessive Daytime Sleepiness (EDS) and hypersomnia

Excessive Daytime Sleepiness (EDS) and sleep complaints are more common children with epilepsy. Maganti et al [22] conducted a study in which children with and without epilepsy between ages 8 and 18 were recruited for the study. Parents and children were asked to fill out the Pediatric Sleep Questionnaire (PSQ) and Pediatric Daytime Sleepiness Scale (PDSS), respectively. Their result showed that parents of children with epilepsy more often reported EDS, symptoms of sleep-disordered breathing, and parasomnias compared with controls. On the PDSS, children with epilepsy reported worse

daytime sleepiness scores compared with controls. Based on conditional logistic regression modeling, symptoms of excessive daytime sleepiness and parasomnias were significantly associated with having epilepsy when adjusted for duration of nigh-time sleep. They concluded that daytime sleepiness appears to be common in children with epilepsy, and may be due to underlying sleep disorders.

Parasomnia

Parasomnia is one the common sleep disorders characterized by abnormal and unusual behaviors, perceptions, movements, feelings or dreams during sleep. Parasomnia is common in children with epilepsy. Bisulli et al [23] reported that in patients with NFLE, 30% have arousal parasomnia and 12% have REM behavioral disorder. The onset of parasomnia is typically seen in children younger than 10 years of age whereas nocturnal seizures start later in life. The parasomnia events are longer, have different behavior patterns, occur during earlier part of the night, originate during stage 3 NREM sleep. On the contrary, nocturnal seizures are brief, highly stereotypic, may occur multiple times throughout the night, usually during stage 1 and stage 2 NREM [24]. The parasomnia somnambulism, night terrors, sleep talking, and probable RBD were more frequently reported in epilepsy patients. Sleep paralysis, however, was more frequent in the healthy group. The higher frequency of these parasomnias in epilepsy patients was not statistically significant, but probable RBD was almost significantly higher in epilepsy patients (12% vs. 6% in healthy controls). The severity of epilepsy did not increase the risk of probable RBD in patients with epilepsy. Nocturnal seizures, especially those arising from the anterior mesial frontal lobe, cingulate gyrus and orbitofrontal cortex, may exhibit bizarre behavior resembling parasomnias. Such patients may not have detectable interictal sharp waves or ictal patterns on scalp electroencephalographic recordings. Typically, seizures are very stereotyped with characteristic semiology of shorter duration and much more frequent than parasomnias that tend to last several minutes and usually occur 1 or 2 times per night. A recent review of paroxysmal motor events during sleep examines this in much more detail.

Restless Legs Syndrome (RLS)

Restless Legs Syndrome (RLS) is a common neurological movement disorder occurring in approximately 10% of the general population. The prevalence of moderately severe RLS is 2.7% overall. Geyer et al [25] evaluated the severity and frequency of primary RLS in patients with localization-related Temporal Lobe Epilepsy (TLE) and investigated the role of prodromal RLS symptoms as a warning sign and lateralizing indicator. All epilepsy patients seen in the outpatient clinic were screened for movement disorders from 2005 to 2015. Ninety-eight consecutive patients with localization-related TLE (50 right TLE and 48 left TLE) who met inclusion criteria were seen in the outpatient clinic. The control group consisted of 50 individuals with no history or immediate family history of epilepsy. They identified frequent moderate to severe RLS in patients with epilepsy. The frequency of RLS was much more common than would typically be seen in patients of similar age. The restlessness was typically described as moderately severe. The RLS symptoms were more common and somewhat more severe in the right TLE group than the left TLE group.

Sleep-Related Epilepsy Syndrome

Sleep plays an important role in the disease process of epilepsy [26]. Sleep has a strong influence on IEDs and seizures [27]. It is well documented that nocturnal seizures occur frequently in stage 2 NREM sleep, followed by stage 1 and then stage 3 and 4 NREM sleep [28]. They are least frequent during REM sleep [29]. Secondary generalization of complex partial seizures is more likely to occur during sleep rather than during wakefulness [30]. Gowers in 1885 [26] noted that nocturnal seizures tended to occur in 2 peaks: one between 9 pm and 11 pm and another peak between 3 am and 5 am. Myoclonic and grand mal seizures in juvenile myoclonic typically occurred in the morning hours, soon after awakening, hence the term "awakening grand mal epilepsy" The tonic seizures of Lennox-Gastaut syndrome are more frequent during sleep and may be quite subtle. REM sleep appears to have an inhibitory effect on these tonic seizures. Frequent tonic seizures during sleep are thought to indicate an unfavorable prognosis. Absence seizures are conspicuous by their virtual absence during sleep, although eyelid fluttering or rarely absence status may occur out of sleep. Similarly, psychogenic seizures do not occur out of sleep; those that occur at night have been shown to be preceded by a period of wakefulness. Seizures in benign focal epilepsy of childhood typically occur during the first 2 hours of sleep in 80% of patients, less often after awakening or during naps. For the most part, the semiology of seizures recorded during sleep resembles those recorded during wakefulness except for greater tendency toward secondary generalization.

Benign Epilepsy with Centro Temporal Spikes (BECTS)

BECTS is a genetic disorder of childhood, characterized by nocturnal generalized seizures of probably focal onset and diurnal partial seizures arising from the lower rolandic area. Characteristic seizures in this syndrome are motor impairment of the face and motor aphasia without impairment of consciousness. The seizures occur more often at night during sleep and day time seizures are rare in the syndrome. It has a characteristic EEG pattern with a mid-temporal-central spike focus and dramatic increasing frequency during drowsiness and sleep. Increased risk of sleep problems in BECTS have been reported. Gogue et al [31] conducted a study that included 15 children with BRE and 27 healthy children who underwent overnight polysomnography. The author found that patients and controls did not differ in basic epidemiological traits. The percentage of sleep stage rapid eye movement was significantly lower in the epilepsy group. Moreover, the mean value of the obstructive apnea index and the obstructive apnea–hypopnea index was significantly higher in children with BRE compared with healthy children. In another report, Tang et al [32] compared parent-reported sleep behaviors of 43 children with BECTS aged 6 to 16 years recruited from 5 US pediatric neurology centers with a historical reference and sleep clinic sample using the Child Sleep Habits Questionnaire. The authors compared the differences in mean frequency of sleep problems and patterns. Total Children's Sleep Habits Questionnaire scores were significantly higher in the BECTS sample than reference. Parents of children with BECTS reported a significantly shorter sleep duration, more frequent parasomnias, and increased daytime sleepiness. They concluded that parents of children with BECTS reported more problematic sleep and daytime impairment compared with a reference sample of children [32].

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)

ADNFLE is a genetic epilepsy syndrome with nocturnal seizures during sleep. Some people with ADNFLE also have seizures during the day. The seizures characteristic of ADNFLE tend to occur in clusters, with each one lasting from a few seconds to a few minutes. Some people have mild seizures that simply cause them to wake up from sleep. Others have more severe episodes that can include sudden, repetitive movements such as flinging or throwing motions of the arms and bicycling movements of the legs. The person may get out of bed and wander around, which can be mistaken for sleepwalking. The person may also cry out or make moaning, gasping, or grunting sounds. These episodes are sometimes misdiagnosed as nightmares, night terrors, or panic attacks. Some patients have aura such as tingling, shivering, a sense of fear, dizziness (vertigo), and a feeling of falling or being pushed. Some affected people have also reported a feeling of breathlessness, overly fast breathing (hyperventilation), or choking. It is unclear what brings on seizures in people with ADNFLE. Episodes may be triggered by stress or fatigue, but in most cases the seizures do not have any recognized triggers. The age of seizure onset varies from infancy to mid-adulthood, but most begin in childhood. The episodes tend to become milder and less frequent with age. In most affected people, the seizures can be effectively controlled with medication. Most people with ADNFLE are intellectually normal, and there are no problems with their brain function between seizures. However, some people with ADNFLE have experienced psychiatric disorders (such as schizophrenia), behavioral problems, or intellectual disability. It is unclear whether these additional features are directly related to epilepsy in these individuals. Additionally, sleep problems are common in this epilepsy syndrome. Vignatelli et al [33] examined patients with ADNFLE at a single epilepsy center and matched controls randomly selected from the general population self-administered questionnaires on daytime sleepiness-related symptoms and subjective sleep quality ESS, BQS, Berlin questionnaire. They found that thirty-three patients with ADNFLE and 27 controls were enrolled. The authors found that patients with ADNFLE have no pathological level of EDS with respect to controls. However, daytime sleepiness-related symptoms could be more frequent in a subgroup of patients with subjective disturbed sleep quality, irrespective of the perceived frequency of seizures.

West Syndrome (WS)

WS is a severe epilepsy syndrome composed of the triad of infantile spasms, hypsarrhythmia on EEG, and mental retardation. West syndrome is an age-specific disorder, beginning primarily in the first year of life with the peak age of onset between 4-6 months. The duration of an epileptic spam is immediate between a myoclonic jerk and a tonic seizure. Spasms often occur in clusters of head nods, forceful flexion, or extension of trunk and limbs. These seizures frequently occur during sleep transitions, especially on awakening. Hypsarrhythmia is seen predominantly in NREM sleep and sometimes visible only in sleep. Pseudo-burst suppression patterns are common during sleep.

Benign Occipital Epilepsy (BOE)

BOE, also known as benign focal epilepsy with occipital paroxysm, is a hereditary type of epilepsy that represents about 3 percent of all childhood epilepsy cases. There is a somewhat higher incidence in girls than in boys. This type of epilepsy can be grouped into two categories, depending on the age of the child when seizures begin. Panayiotopoulos type begins between 15 months and 17 years. Seizures are infrequent and typically occur at night, shortly after the child falls asleep. Episodes usually last less than 10 minutes and may include vomiting and gazing toward one side, and frequently evolve to rhythmic muscle contractions on one or both sides of the body. Triggers may include turning off lights, going from lighted areas to dark ones, or from dark areas to light ones. Gastaut type begins between the ages of 3 and 16 years and has a peak onset between ages 7 and 9. Children may experience visual hallucinations with the seizure. Headaches are common before, during, or after the seizures. Most seizures (70%) occur during sleep and 17% during wakefulness and 13% upon awakening.

Electrical Status Epilepticus During Slow Sleep/ Continuous Spike Wave Discharges During Sleep (ESES/ CSWS)

ESES/CSWS is an age-dependent syndrome with the characteristic pattern of continuous spike and waves during non-rapid eye movement sleep. Most children can present developmental deterioration. The demonstration of the EEG pattern has to rely on all night long EEG recordings. The terms Continuous Spike Wave in Slow-Wave Sleep (CSWS) and Landau-Kleffner Syndrome (LKS) describe the clinical epileptic syndromes seen with ESES. Although there is an overlap between these 2 syndromes, children with CSWS present with a more global regression have more problematic epilepsy and have EEG foci located predominantly in frontotemporal or frontocentral regions. In contrast, children with LKS present with an acquired auditory agnosia, fewer seizures, and EEG foci in the posterotemporal regions. ESES requires a high degree of clinical suspicion because slow-wave sleep must be recorded to confirm this diagnosis. Treatment of ESES extends beyond just control of the seizures; amelioration of the continuous epileptiform discharge must occur to improve neuropsychological outcome. Although there is little evidence to guide treatment, conventional antiepileptic drugs play only a minimal role. Steroid therapy and high-dose benzodiazepines are most commonly used, but other therapies including intravenous gamma-globulin, the ketogenic diet, and surgical therapy with multiple subpial transaction have shown efficacy in small case series [34]. Although epilepsy resolves with time in most cases, many children are left with significant cognitive or language impairment. Longer duration of ESES appears to be the major predictor of poor outcome; markedly abnormal neuronal activity during a critical period for synaptogenesis may result in aberrant synapse formation, explaining the poorer neuropsychological outcome. Early recognition and effective therapy are necessary to improve long-term prognosis in this condition. Patients with unilateral brain lesion and ESES can be treated successfully with epilepsy surgery. Lodden kemper et al in 2009 [35] reported a study in which eight patients were included. All patients presented with medically refractory epilepsy, hemiparesis, and developmental delay. The pathogenesis was perinatal infarction in 7 patients and malformation of cortical development in 1 patient. Preoperative electroencephalography demonstrated generalized interictal spikes, electroencephalographic seizures, and ESES in all cases. Age at the time of surgery ranged from 3 to 14 years. Six patients underwent hemispherectomy, and 2 patients underwent focal

resection. Six patients became seizure-free after resection. Two patients with functional hemispherectomy continued to have rare seizures, but were much improved. These patients also had perinatal infarctions in the hemisphere contralateral to the resection, possibly indicating a less beneficial outcome. Postoperative electroencephalography demonstrated resolution of generalized interictal discharges and ESES in all. Formal pre and postoperative neuropsychological testing showed overall improvement of age-equivalent scores. This result showed that children with unilateral brain lesions and seizures may become seizure-free after epilepsy surgery, even if the preoperative electroencephalogram shows generalized ESES. The lesion occurring early in life and the location of the lesion may play a role in the development of ESES. Cognitive impairment may be aggravated by the persistence of ESES. Preliminary developmental data in this small sample suggest that termination of seizures and possibly of ESES by epilepsy surgery may have developmental benefits.

Juvenile Myoclonic Epilepsy (JME)

JME is the most common of the generalized epilepsy syndromes to emerge in mid-to-late childhood. It is characterized by the presence of absence (formerly called petit mal) seizures, myoclonic seizures and generalized tonic-clonic (formerly called grand mal) seizures. Typically, the first seizure type to present are absence seizures - these start anywhere between the ages of 5 and 16 years of age. Myoclonic jerks are seen about 1 to 9 years later, with an average age of 14 or 15 years. Generalized tonic-clonic seizures appear a few months later after that, although they can appear earlier [36]. Both males and females are affected equally. The hallmark of juvenile myoclonic epilepsy and grand mal seizures on awakening are seizure symptoms within 2 hours after awakening, often provoked by sleep deprivation. In addition, JME is associated with significant sleep problems. Altered polysomnography profile was reported in JME patients. Krishnan et at [37] conducted a prospective cross-sectional case-control study involved 25 patients of JME on valproic acid and 25 matched healthy controls were recruited. All patients underwent clinical assessment, Electroencephalogram (EEG), and evaluation with sleep questionnaire and PSG. Their result revealed significant alterations in sleep architecture in the JME group in the form of reduced mean sleep efficiency and number of patients with reduced sleep efficiency, increased mean sleep onset latency and number of patients with increased sleep latency, reduced mean Stage 2 sleep percentage and reduced mean total NREM (non-rapid eye movement) sleep and increased mean wake percentage. The frequency of arousals, involuntary limb movements, and event related arousals in the JME groups was not different from the controls. They concluded significant alterations in sleep architecture in JME despite adequate seizure control. There was variable degree of PSG-phenotypic correlation.

Effects of Epilepsy Treatments on Sleep Disorders

Evident has been accumulated showing epilepsy treatments including antiepileptic drugs, epilepsy surgery, ketogenic diet and vagus nerve stimulator have different effects on sleep disorders in patients with epilepsy. Jain and Glauser conducted an evidence-based review and identified that gabapentin, tiagabine, pregabalin, clobazam, and carbamazepine reduce sleep latency and/or improve sleep efficiency. Phenobarbital, valproic acid, and higher-dose levetiracetam aggravate daytime sleepiness, whereas topiramate and zonisamide do not. Epilepsy surgery may improve nocturnal sleep only in a subgroup of patients with improved seizure frequency. ketogenic diet improves slow-wave sleep [38].

Vagus nerve stimulator has been used to control intractable epilepsy since 1990 [39] and it was approved as an adjective therapy for intractable epilepsy in 1997.It has been shown to reduce seizures by 50% in adults and up to 90% in pediatric epileptic patients [40]. Vagus nerve stimulator has been reported to decrease airflow, oxygen saturation and respiratory amplitude during sleep [41]. In a recent case report, Joutsa et al reported two patients had sleep apnea likely caused by vagus nerve stimulator since the apnea resolved by changing the setting of the stimulator [42]. Upadhyah et al reported report a pediatric patient in whom OSA improved after tonsillectomy, but coexistent VNS-induced SDB persisted. With decrease in VNS output current, patient's SDB improved, but seizure activity exacerbated, which required a return to the original settings. Continuous positive airway pressure titration was attempted, which showed only a partial improvement in apnea-hypopnea index. This case illustrates the need for clinicians to balance seizure control and SDB in patients with VNS [43]. In a recent review, parhizgar et al provided evidence showing that Patients with VNS can have central apneas, obstructive hypopneas, and obstructive apneas. These respiratory events can be reduced with changes in the vagus nerve stimulator operational parameters or with the use of CPAP. They conclude that there are complex relationships between epilepsy and obstructive sleep apneas. In particular, patients with refractory epilepsy need assessment for undiagnosed and untreated obstructive sleep apnea before implantation of vagus nerve stimulator devices. Patients with vagus nerve stimulators often have an increase in apneic events after implantation, and these patients need screening for sleep apnea both before and after implantation [44].

Basic Mechanisms Influencing Sleep and Epilepsy

It is known that neuronal networks of oscillations play an important role in the generation of sleep and epileptic seizures [45]. It is also believed that thalamus is the pacemaker for spindle rhythms in sleep and generalized spike and wave discharges in epilepsy [46]. The corticothalamic system is modulated by the brain stem and basal forebrain. This system is comprised of the cortical neurons, dorsal thalamic nuclei, and Reticular Nucleus of the Thalamus (RE). Sleep oscillations are suppressed during wakefulness by input from various ascending cholinergic, monoaminergic and glutaminergic system. At sleep onset, neurons in the midbrain reticular formation and midpons reduce their firing rate; the reduced excitatory input allows cortical and thalamocortical neurons to become more hyperpolarized, in turn leading to reduced synaptic input. Further hyperpolarization of the thalamic RE cells and de-inactivation of low-threshold Ca++ spikes leads to the appearance of sleep spindles [47]. Bursts in thalamic reticular neurons produce powerful inhibition in thalamic relay neurons via activation of via both GABA-A and GABA-B mediated transmissions. GABA-A receptor mediated chloride-dependent IPSP in the thalamus has mainly been associated with the inhibitory modulation of sensory and cortical flow whereas GABA-B receptor-mediated IPSPs in the thalamus mainly "prepare" thalamocortical cells for busting by activating low-threshold calcium potentials. These anatomical and neurochemical features within thalamus determine the generation and spread of spindle rhythm in sleep [48].

Same networks and mechanisms within the thalamus are implied in the generation of 3 Hz spike and wave discharges in epileptic seizures. Microinjection of GABA and GABA-B agonist in the reticular nuclei in the thalamus aggravate generalized spike and wave discharges in an animal model of absence seizures [49]. These mechanisms include robust burst-firing capability of thalamic neurons, recurrent excitatory and inhibitory synaptic connectivity, and long-lasting and powerful inhibitory synaptic responses arising from activity in thalamic reticular neurons and mediated by Gamma-Amino Butyric Acid (GABA) receptors. The 3 Hz thalamic synchronization appears to arise from a perturbation of a physiologic, higher frequency spindle oscillation. Two currently available anti absence medications interact with this circuitry with the net result of decreased synchronization, largely through reduction in inhibitory output from the thalamic reticular nucleus. Ethosuximide blocks T-type calcium channels and thus reduces the ability of thalamic neurons to fire bursts of spikes, thereby reducing inhibitory (and excitatory) output within the circuit [50].

Hodaje et al [51] showed that single unit microelectrode recordings were obtained under local anesthesia in 5 patients who underwent placement of deep brain stimulation electrodes in the anterior thalamic nucleus for control of intractable epilepsy. Of the 261 neurons recorded, 145 were in the Anterior Nucleus (AN), with the remainder ventral to AN in nucleus cucularis and dorsal Dorsomedian Nucleus (DM). 126 of the 261 neurons fired in bursts. The bursts in 70% of the bursting neurons were characterized as Low-Threshold Calcium Spike (LTS) mediated bursts. LTS and atypical bursting cells were found both within AN and in the nucleus cucularis and dorsal DM. The LTS bursting observed in these patients may be due to the altered electrophysiological state of the patients studied since LTS bursting in thalamus is usually only observed during sleep. This study describes for the first time the properties of this nucleus in humans and may be important in furthering our knowledge of thalamic mechanisms of epileptogenesis.

These evidences support that common neuronal networks exist in the brain, particularly in the thalamus are involved in both sleep and epilepsy. Alterations in function of these neuronal networks are likely cause sleep disorders and epilepsy.

Conclusion

Sleep disorders are common in children, especially in children with epileptic disorders. There is a bidirectional relationship between childhood sleep disorders and childhood epileptic disorders. Sleep disorders can aggravate IEDs and nocturnal seizures in children with epilepsy, leading to poor seizure control and increasing functional disturbance; On the other hand, childhood epileptic disorders can change sleep quality and architecture of sleep, resulting in an increase in light sleep and reduction of REM sleep, which can lead to sleep disorders. In patients with childhood epileptic disorder, sleep architecture and the restorative functions of sleep are compromised by seizures, IEDs, and antiepileptic drugs. Recognizing and effectively treating sleep disorders in patients with childhood epileptic disorders can improve seizure control and overall functioning. The diagnostic evaluation of nocturnal events benefits from a collaborative approach by epilepsy and sleep specialists and utilization of video-EEG polysomnography for accurate diagnosis both disorders. Despite the complexity of this relationship, the prognosis is a favorable if proper treatments are provided to address both disorders. Clinicians need to be vigilant about asking about and addressing sleep complaints in patients with epilepsy and vice versa.

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