



Should we be targeting the sleep–wake patterns of children with epilepsy?



Sejal V Jain¹



Sanjeev V Kothare*

“...the treatment of coexisting sleep disorders can potentially improve both QOL and seizure control in children with epilepsy.”

Epilepsy affects 1% of the general population [1]. The interaction between sleep and epilepsy has been well known since the times of Aristotle. Fragmented sleep causes daytime fatigue and poor seizure control, while uncontrolled seizures and epilepsy can worsen sleep quality. Moreover, both sleep disruption and epilepsy negatively affect overall quality of life (QOL). In this article, we discuss the existing literature and provide future initiatives needed to improve sleep and epilepsy along with overall QOL.

What do we know?

Non-rapid eye movement sleep, via synchronization of neuronal circuits, activates interictal epileptiform discharges (IEDs) and seizures; both occur predominantly in N1 and N2 sleep in children [2]. However, in desynchronized rapid eye movement (REM) sleep, seizures and IEDs are very uncommon. Additionally, seizure occurrence is nonrandom, dependent on underlying circadian rhythms. Temporal lobe

seizures (TLS) occur during wakefulness, while frontal lobe seizures (FLS) occur in sleep. Sleep–wake state rather than day–night timing is a better predictor of these seizures [3].

Conversely, seizures and epilepsy also influence sleep [2]. Patients with epilepsy have abnormal sleep architecture, including reduced N2 and N3 sleep and increased N1 sleep and REM latency. Additionally, reduced sleep spindle density and abnormal K-complex morphology is observed. Seizures occurring in sleep deteriorate the quality of sleep by increasing N1 and N2 sleep, at the cost of N3 and REM sleep. Interestingly, REM sleep rebounds with good seizure control.

Antiepileptic drugs (AEDs) also modify sleep [2]. Barbiturates, benzodiazepines, phenytoin and carbamazepine decrease REM sleep and increase daytime drowsiness. Valproic acid causes daytime drowsiness with minimal effects on sleep architecture. Gabapentin and tiagabine improve

“Fragmented sleep causes daytime fatigue and poor seizure control, while uncontrolled seizures and epilepsy can worsen sleep quality.”

¹Division of Neurology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, MLC 2015, Cincinnati, OH 45229, USA

*Author for correspondence: Division of Epilepsy & Clinical Neurophysiology, Harvard Medical School, Children's Hospital Boston, Fegan 9, 300 Longwood Ave, Boston, MA 02115, USA; Tel.: +1 617 355 5606; Fax: +1 617 730 0463; sanjeev.kothare@childrens.harvard.edu

“Forced desynchronization of circadian rhythms by changing sleep times can activate seizures when needed, especially during presurgical evaluation.”

sleep by improving sleep efficiency and N3 sleep. Lamotrigine decreases N3 but increases N2 sleep and, similar to felbamate and ethosuximide, also causes insomnia. Levetiracetam may consolidate sleep. Finally, vagus nerve stimulation improves daytime alertness without affecting sleep.

Some epilepsy syndromes with seizures related to sleep states are considered sleep-related epilepsies [2]. Seizures in nocturnal frontal lobe epilepsy are brief, multiple and present with bizarre motor phenomena in sleep. Seizures of benign rolandic epilepsy occur in sleep, involving one side of the face or limb. In juvenile myoclonic epilepsy, seizures occur around awakening and consist of myoclonic jerks and generalized seizures. Additionally, parasomnias often coexist and are sometimes difficult to differentiate from FLS due to similar semiology and the absence of EEG changes in the latter.

Sleep problems have been increasingly recognized in children with epilepsy [4]. In children with a first-recognized seizure, 45% reported sleep problems. Moreover, the quality of sleep is worse with refractory seizures and polytherapy use.

Among the sleep disorders, obstructive sleep apnea (OSA) is most commonly observed in patients with epilepsy. A third of the patients with refractory epilepsy have OSA. In a study of children with epilepsy referred for a sleep study, OSA was found in 42% and periodic limb movement disorder (PLMD) was found in 10% [5]. The relationship of central sleep apnea to seizures has recently received attention. Central sleep apnea and the cardiorespiratory abnormalities accompanying certain epilepsies may help to understand the mechanisms for sudden unexplained death in epilepsy (SUDEP) [6]. Mortality from SUDEP is 40–200-times more prevalent than in the general population [7].

Sleep deprivation is the most common seizure-precipitating factor. Not only poor sleep quality, but also reduced sleep duration, worsens seizure control. A total of 1 h of additional sleep decreases the relative odds of a daytime seizure to 0.91 (95% CI: 0.82–0.99) [8]. Furthermore, treatment of OSA and PLMD can also improve seizure control [9]. This in turn can improve daytime behaviors and QOL [10]. Hence, early identification and treatment of sleep disturbances in patients with epilepsy is important.

What do we not know?

Even though we are aware of the complex relationship between sleep and epilepsy, a lot still

remains unknown. Why do sleep and sleep deprivation activate epileptiform discharges and seizures? Although several mechanisms are suggested [2], definite proof has yet to emerge. We need to develop multicenter studies to identify better treatment strategies and assess the impact of treatment on QOL, cognition, behavior and seizure control.

What should we do?

■ What should we have done yesterday?

Increase awareness

Increasing the awareness of the coexistence of sleep disorders in the epilepsy population among the providers and families is the first step. This can be achieved by organizing educational talks at the national, regional and local level, as well as publishing more data on the subject.

■ What should we be doing today?

Identify the prevalence of sleep disorders

The precise knowledge on the prevalence of sleep disorders in the epilepsy population will help us to appropriately diagnose, treat and channel funds into research on the subject. To achieve this, patients should be screened for sleep disorders using questionnaires. Currently, existing sleep questionnaires include the Pediatric Sleep Questionnaire (PSQ), Child Sleep Habits Questionnaire (CSHQ), Cleveland Adolescents Sleep Questionnaire (CASQ) and the Pediatric Daytime Sleepiness Scale (PDSS). Using the PSQ, 45% of children with refractory epilepsy were identified as being at risk of OSA [11]. These children can then be referred to the sleep clinic for further evaluation, and if necessary, polysomnography to confirm the diagnosis.

Identifying treatment strategies

AEDs can be selected based on their side-effect profile. Medications such as barbiturates and benzodiazepines can be used to improve insomnia, while lamotrigine, felbamate and ethosuximide can be used to counteract daytime drowsiness, and can be given earlier in the evening rather than at bedtime so as to not worsen insomnia. Tiagabine and gabapentin can be used to consolidate sleep. Additionally, the circadian pattern of seizure occurrence can guide the timing of higher dosing of AEDs around seizure peaks. For example, in patients with nocturnal frontal lobe epilepsy or juvenile myoclonic epilepsy, higher evening doses and small morning

doses can achieve better seizure control and also improve daytime alertness [12].

Patients with epilepsy are often predisposed to coexisting OSA. AEDs such as valproate, gabapentin, carbamazepine and vigabatrin may cause weight gain, and some, such as benzodiazepines and barbiturates, may affect the upper airway muscle tone, with resultant higher risk for OSA. Additionally, OSA is reported with vagus nerve stimulator use [13]. Thus, these treatments should be used cautiously in children with risk factors or pre-existent OSA. Appropriate screening and, if needed, treatment should be attempted for coexisting OSA in this population.

Despite limited data, melatonin has been extensively used as a hypnotic to treat insomnia in epilepsy. In addition, little information is available on the use of hypnotic medications in children. As sleep-onset and sleep-maintenance problems are common in children with epilepsy, randomized double-blind studies to assess the safety, efficacy and dosing of hypnotics in this population are needed.

AEDs such as gabapentin and pregabalin are effective in the treatment of PLMD. Hence, partial epilepsy and coexisting PLMD can be treated with the use of one medication.

Impact on seizure control & QOL

A recent randomized study showed that effective treatment of coexisting OSA improves overall seizure control [9]. Additionally, nocturnal melatonin improved QOL in children with sleep problems and epilepsy in another study [14]. Hence, the treatment of coexisting sleep disorders can potentially improve both QOL and seizure control in children with epilepsy.

SUDEP

SUDEP is not uncommon, yet remains poorly understood [7]. Understanding the underlying mechanisms and improving treatment strategies should be undertaken to reduce SUDEP.

■ What should we do tomorrow?

Chronobiology & diagnostic & therapeutic opportunities

Circadian rhythms can modify epilepsy. The effect of endogenous melatonin on epilepsy is complex; it is reduced in intractable epilepsy, and increased postictally, suggesting its anti-convulsant properties. On the other hand, it may act as a proconvulsant at higher doses in mesial

temporal sclerosis [15]. Interestingly, complex partial seizures were less likely to occur during bright sunny days than on days with reduced sunlight [16]. Endogenous melatonin secretions are postulated as possible mechanisms for this observation. Furthermore, TLS occur 0–6 h prior to dim light melatonin onset, while FLS occur 6–12 h after dim light melatonin onset [17]. Finally, when patients with generalized epilepsy were allowed to have free-running circadian rhythms, IEDs showed a circadian variability, independent of sleep [18].

These preliminary observations offer opportunities for new diagnostic and treatment modalities. Forced desynchronization of circadian rhythms by changing sleep times can activate seizures when needed, especially during pre-surgical evaluation. In addition, the circadian pattern of seizures may assist in the identification and localization of specific epilepsy syndromes; FLS occur in sleep and TLS occur in wakefulness. An ongoing study is assessing the use of light therapy to improve seizure control, treat coexisting depression and improve the QOL in subjects with epilepsy [19].

Memory, sleep & epilepsy

Cognitive impairment is reported in 25% of children with epilepsy. Even in presumed ‘benign’ rolandic epilepsy, neuropsychological tests have identified deficits in cognition, behavior and attention [20]. Sleep has been shown to help memory consolidation. As children with epilepsy commonly have sleep disturbances, cognition and memory may presumably improve if sleep improves. Further studies are needed to assess this theory.

Conclusion

Sleep and epilepsy are ‘common bedfellows’. Further studies will help us understand this better, and eventually improve the overall care of children with epilepsy.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

“...the circadian pattern of seizures may assist in the identification and localization of specific epilepsy syndromes; FLS occur in sleep and TLS occur in wakefulness.”

References

- 1 Hauser WA, Annegers JF, Kurland LT. Prevalence of epilepsy in Rochester, Minnesota. 1940–1980. *Epilepsia* 32(4), 429–445 (1991).
- 2 Kothare SV, Kaleyias J. Sleep and epilepsy in children and adolescents. *Sleep Med.* 11(7), 674–685 (2010).
- 3 Loddenkemper T, Vendrame M, Zarowski M *et al.* Circadian patterns of pediatric seizures. *Neurology* 76(2), 145–153 (2011).
- 4 van Golde EG, Gutter T, de Weerd AW. Sleep disturbances in people with epilepsy; prevalence, impact and treatment. *Sleep Med. Rev.* 15(6), 357–368 (2011).
- 5 Kaleyias J, Cruz M, Goraya JS *et al.* Spectrum of polysomnographic abnormalities in children with epilepsy. *Pediatr. Neurol.* 39(3), 170–176 (2008).
- 6 Tezer FI, Remi J, Noachtar S. Ictal apnea of epileptic origin. *Neurology* 72(9), 855–857 (2009).
- 7 Meyer S, Shamdeen MG, Gottschling S, Strittmatter M, Gortner L. Sudden unexpected death in epilepsy in children. *Forensic Sci. Med. Pathol.* 47(6), 326–331 (2011).
- 8 Haut SR, Hall CB, Masur J, Lipton RB. Seizure occurrence: precipitants and prediction. *Neurology* 69(20), 1905–1910 (2007).
- 9 Malow BA, Weatherwax KJ, Chervin RD *et al.* Identification and treatment of obstructive sleep apnea in adults and children with epilepsy: a prospective pilot study. *Sleep Med.* 4(6), 509–515 (2003).
- 10 Stores G, Wiggs L, Campling G. Sleep disorders and their relationship to psychological disturbance in children with epilepsy. *Child Care Health Dev.* 24(1), 5–19 (1998).
- 11 Jain SV, Simakajornboon S, Shapiro SM, Morton LD, Leszczyszyn DJ, Simakajornboon N. Obstructive sleep apnea in children with epilepsy: prospective pilot trial. *Acta Neurol. Scand.* doi:10.1111/j.1600-0404.2011.01506.x (2011) (Epub ahead of print).
- 12 Guilhoto LM, Loddenkemper T, Vendrame M, Bergin A, Bourgeois BF, Kothare SV. Higher evening antiepileptic drug dose for nocturnal and early-morning seizures. *Epilepsy Behav.* 20(2), 334–337 (2011).
- 13 Khurana DS, Reumann M, Hobdell EF *et al.* Vagus nerve stimulation in children with refractory epilepsy: unusual complications and relationship to sleep-disordered breathing. *Childs Nerv. Syst.* 23(11), 1309–1312 (2007).
- 14 Gupta M, Aneja S, Kohli K. Add-on melatonin improves sleep behavior in children with epilepsy: randomized, double-blind, placebo-controlled trial. *J. Child Neurol.* 20(2), 112–115 (2005).
- 15 Banach M, Gurdziel E, Jedrych M, Borowicz KK. Melatonin in experimental seizures and epilepsy. *Pharmacol. Rep.* 63(1), 1–11 (2011).
- 16 Baxendale S. Seeing the light? Seizures and sunlight. *Epilepsy Res.* 84(1), 72–76 (2009).
- 17 Hofstra WA, Gordijn MC, van der Palen J, van Regteren R, Grootemarsink BE, de Weerd AW. Timing of temporal and frontal seizures in relation to the circadian phase. A prospective pilot study. *Epilepsy Res.* 94(3), 158–162 (2011).
- 18 Pavlova MK, Shea SA, Scheer FA, Bromfield EB. Is there a circadian variation of epileptiform abnormalities in idiopathic generalized epilepsy? *Epilepsy Behav.* 16(3), 461–467 (2009).
- 19 Loddenkemper T, Lockley SW, Kaleyias J, Kothare SV. Chronobiology of epilepsy: diagnostic and therapeutic implications of chrono–epileptology. *J. Clin. Neurophysiol.* 28(2), 146–153 (2011).
- 20 Parisi P, Bruni O, Pia Villa M *et al.* The relationship between sleep and epilepsy: the effect on cognitive functioning in children. *Dev. Med. Child Neurol.* 52(9), 805–810 (2010).