Epilepsy Currents
2021, Vol. 21(1) 19-20

DOI: 10.1177/1535759720973269
journals.sagepub.com/home/epi
SAGE

Deep-Seated Interictal Epileptiform Activity: Another Reason to Lose Sleep

Sleep Disruption in Epilepsy: Ictal and Interictal Epileptic Activity Matter

Peter-Derex L, Klimes P, Latreille V, et al. *Ann Neurol*. 2020;88(5):907-920. doi:10.1002/ana.25884. PMID: 32833279.

Objective: Disturbed sleep is common in epilepsy. The direct influence of nocturnal epileptic activity on sleep fragmentation remains poorly understood. Stereo-electroencephalography paired with polysomnography is the ideal tool to study this relationship. We investigated whether sleep-related epileptic activity is associated with sleep disruption. Methods: We visually marked sleep stages, arousals, seizures, and epileptic bursts in 36 patients with focal drug resistant epilepsy who underwent combined stereo-electroencephalography/polysomnography during presurgical evaluation. Epileptic spikes were detected automatically. Spike and burst indices (n/sec/channel) were computed across four 3-second time windows (baseline sleep, prearousal, arousal, and postarousal). Sleep stage and anatomic localization were tested as modulating factors. We assessed the intra-arousal dynamics of spikes and their relationship with the slow-wave component of nonrapid eye movement sleep (NR) arousals. Results: The vast majority of sleep-related seizures (82.4%; 76.5% asymptomatic) were followed by awakenings or arousals. The epileptic burst index increased significantly before arousals as compared to baseline and postarousal, irrespective of sleep stage or brain area. A similar prearousal increase was observed for the spike index in NR stage 2 and rapid eye movement sleep. In addition, the spike index increased during the arousal itself in neocortical channels and was strongly correlated with the slow-wave component of NR arousals ($r = 0.99$, $P < .0001$). Interpretation: Sleep fragmentation in focal drug-resistant epilepsy is associated with ictal and interictal epileptic activity. The increase in interictal epileptic activity before arousals suggests its participation in sleep disruption. An additional increase in the spike rate during arousals may result from a sleep–wake boundary instability, suggesting a bidirectional relationship.

Commentary

The interplay between sleep and epilepsy is multifaceted. Sleep disruption is associated with poor seizure control, and interictal epileptiform activity (EA) is activated during sleep, as shown on long-term electrocorticographic data that are acquired for months to years with a closed-loop implanted neurostimulator system.[1] Conversely, nocturnal seizures can interrupt sleep. This bidirectional interaction is commonly observed in patients with both focal and generalized epilepsy. In cross-sectional studies of patients with focal onset epilepsy, a higher prevalence of subjective sleep disturbances, consisting primarily of insomnia and sleep apnea, was seen compared to normal controls.[2] These disturbances were more common in uncontrolled patients and were associated with severe impairment in quality of life.[3] Additional factors that can affect the quality of sleep in patients with epilepsy include comorbid sleep or mood disorders, medications effects, and nocturnal seizures.[4] Nocturnal seizures can fragment sleep, resulting in a reduction of total sleep time and decreases in slow-wave (SW) and rapid eye movement (REM) sleep. But even in the absence of nocturnal seizures, marked sleep instability and increased nocturnal awakenings have been reported in patients with generalized interictal EA.[5] Most studies that have explored the relationship between epilepsy and sleep have relied on scalp electroencephalogram (EEG) data, with its inherent inability to quantify deep-seated EA. So, what is the temporal relationship between EA, such as the one occurring in mesial temporal structures, and sleep disruption?

In the study by Laure Peter-Derex et al,[6] stereo-EEG (SEEG) was combined with polysomnography (PSG) to evaluate the temporal effect of EA on sleep structure. The authors performed a retrospective evaluation of 36 adult patients with drug-resistant epilepsy and a well-defined seizure-onset zone. Nineteen patients had extratemporal epilepsy (9 with nonlesional magnetic resonance imaging) and 9 of 17 patients with temporal lobe epilepsy had mesial disease. An average of 10 electrodes were implanted stereotactically using an image-guided system, and scalp EEG was obtained from frontal,

central, parietal, and midline leads. On the night of the sleep recording, done at least 72 hours post-implantation, electrooculogram and chin electromyogram were included, and sleep analysis and detection of arousals were done manually. Epileptiform activity was classified as (1) clinical versus subclinical seizures, (2) epileptic bursts (lasting up to 10 seconds), or (3) isolated spikes. Spike and burst indices were computed across time windows during baseline sleep, prearousal, arousal, and postarousal states. Topographic effects of EA on arousals were evaluated and compared between mesial temporal and neocortical channels. Comparisons of sleep parameters were performed among patients with versus without nocturnal seizures and mesial temporal versus other epilepsy.

Twelve patients experienced seizures, 22 had epileptic bursts, and all had spikes. Sleep parameters were normal except for an increase in wake time after sleep onset, which was higher in patients who experienced seizures during the recorded night, independent of the seizure duration. Most sleep-related clinical, and to a lesser degree subclinical, seizures were followed by awakenings (70.6%) or arousals (11.8%). The epileptic burst index increased significantly before arousals, as compared to baseline and postarousal, irrespective of sleep stage, or brain area. In contrast, a prearousal increase was observed for the spike index but was only significant during N2 and REM sleep. Additionally, the spike index increased during the arousal itself in neocortical channels and correlated with non-REM arousals.

Regarding brain area, the spike index increased significantly before the arousal only in mesial temporal channels. In neocortical channels, an increase in the spike index between baseline-TW to arousal-TW was observed during SW sleep compared to non-SW arousals, with the opposite relationship occurring in mesial temporal channels.

These findings indicate that both ictal and interictal EA profoundly disrupt sleep architecture, with sleep disruptions occurring during different sleep phases depending on the location of the activity. Most sleep-related seizures were followed by awakening or arousals, resulting in a substantial increase in waking time after sleep onset. Likewise, interictal EA was also closely linked to arousals. The bidirectional interaction between sleep and epilepsy was evident in the effect of arousal on triggering EA, specifically in neocortical areas.

What are the clinical repercussions of the effects of EA on sleep architecture? Given that sleep fragmentation is associated with daytime sleepiness and decreased psychomotor performance, it is not surprising that patients with nocturnal EA frequently report cognitive difficulties. A recent study of side-specific hippocampal memory function of patients with focal epilepsy, evaluated with SEEG, has reported that retention of verbal memory over 1 week was negatively correlated with hippocampal spike frequency during sleep, whereas no significant correlation was found with hippocampal interictal EA occurring when awake.[7] As highlighted by Laure Peter-Derex et al,[6] not only ictal but also interictal EA occurring in the hippocampus during sleep may impair sleep quality and possibly impact memory consolidation.

Recognition and management of sleep disturbances are important and distinct considerations in patients with epilepsy. Because poor sleep can exacerbate EA, and EA can disrupt sleep, uncontrolled patients with sleep complaints should be evaluated with PSG to assess the presence of a secondary sleep disorder, such as obstructive sleep apnea, which can occur in up to 30% of patients.[8] Additionally, maximizing the control of nocturnal seizures and interictal ED can lead to improvement in sleep-related complaints and cognitive symptoms, as reported in a series of drug-resistant patients who achieved seizure-freedom after undergoing temporal lobectomy.[9] It would be beneficial to explore if suppression of interictal EA through neuromodulation or targeted medication timings can improve the sleep disturbances, and resultant cognitive problems, that occur in so many patients with epilepsy.

By David King-Stephens

ORCID iD

David King-Stephens https://orcid.org/0000-0003-0555-673X

References

1. Spencer DC, Sun FT, Brown SN, et al. Circadian and ultradian patterns of epileptiform discharges differ by seizure-onset location during long-term ambulatory intracranial monitoring. *Epilepsia*. 2016;57(9):1495-1502.
2. de Weerd A, de Hass S, Otte A, et al. Subjective sleep disturbance in patients with partial epilepsy: a questionnaire-based study on prevalence and impact on quality of life. *Epilepsia*. 2004;45(11): 1397-1404.
3. Ismayilova V, Demir AU, Tezer FI. Subjective sleep disturbance in epilepsy patient at an outpatient clinic: a questionnaire-based study on prevalence. *Epilepsy Res*. 2015;115:119-125.
4. Bazil C. Sleep and epilepsy. *Curr Opin Neurol*. 2000;13:171-175.
5. Terzano M, Parrino L, Anelli S, Boselli M, Clemens B. Effects of generalized interictal EEG discharges on sleep stability; assessment by means of cyclic alternating pattern. *Epilepsia*. 1992; 33(2):317-326.
6. Laure Peter-Derex L, Petr Klimes P, Latreille V, Bouhadoun S, Dubeau F, Frauscher B. Sleep disruption in epilepsy: ictal and interictal epileptic activity matter. *Ann Neurol*. 2020;88(5): 907-920. Version of Record online: September 21, 2020.
7. Lambert I, Tramoni-Negre E, Lagarde S, et al. Hippocampal interictal spikes during sleep impact long-term memory consolidation. *Ann Neurol*. 2020;87(6):976-987.
8. Malow BA, Foldvary-Schaefer N, Vaughn BV, et al. Treating obstructive sleep apnea in adults with epilepsy: a randomized pilot trial. *Neurology*. 2008;71(8):572-577.
9. Serafini A, Kuate C, Gelisse P, et al. Sleep before and after temporal lobe epilepsy surgery. *Seizure*. 2012;21(4):260-265.