Sleep Deprivation and Seizures: What is the Evidence?

Jocelyn Y Cheng
NYU Comprehensive Epilepsy Center,
USA

COLUMN ARTICLE

The occurrence of a seizure, either *de novo* or in people with epilepsy (PWE), confers significant social, economic, and health-related burden. For a patient without a prior history of epilepsy, this can include limitations on driving privileges and the extensive evaluations required for accurate diagnosis. In PWE, the presence of any seizures, regardless of frequency, are associated with poorer quality of life [1,2]. Thus, factors which may provoke a seizure, especially if preventable, are important to identify. To that end, at least one seizure precipitant is identified in up to 91% of PWE, among which one of the most commonly reported is sleep deprivation (SD) [3].

Multiple clinical reports have demonstrated an association between SD and seizures. At one epilepsy center, SD was the second most common seizure precipitant identified by patients, reported in 27% of temporal lobe epilepsies and 28% of generalized epilepsies [4]. In a series of 14 temporal lobe epilepsy patients followed for two years, daily diaries were reviewed for duration of sleep per night and date of seizures. When SD was present (defined as > 1.5 hours less than mean sleep), the probability of seizures occurring within 48 hours was 0.09 per 100 nights for normal sleep versus 0.58 for sleep deprived nights [5]. Similarly, another series in which focal epilepsy patients completed seizure diaries demonstrated that for each hour of increased sleep

on the preceding night, the relative odds of a seizure the following day decreased. In addition, when patients self-predicted the likelihood of a seizure the next day, hours of sleep for the night prior to the seizure remained significant, even after adjusting for the seizure risk factors of stress and anxiety, thus demonstrating that patient-reported SD as a seizure precipitant may be reliable [6]. Other series, however, have not shown an association between SD and seizures. In a study of 84 patients with medically refractory focal epilepsy admitted to an epilepsy monitoring unit (EMU), seizure frequency during simulated SD (awake from 10 PM to 6 AM every other night) and normal sleep (awake 6 AM to 10 PM) was assessed. Seizures per day for focal impaired, bilateral tonic clonic and both seizure types, calculated from admission until the end of the protocol, did not differ significantly between the two groups [7]. The objective measures of this study attest to its accuracy, which may not be the case for patient-reported assessments; however, it can also be argued that the SD protocol utilized was not representative of a true SD condition.

Evidence for the association between SD and seizures using measures of greater objectivity also exists. In a prospective study of 114 PWE with normal baseline EEGs, there was a 41% activation rate (defined as percent of studies with new abnormalities) after SD. The activation rate was similar for those with generalized tonic clonic, (41%), focal impaired awareness (47%), and focal motor seizures (37% activation). When a third EEG was repeated after a

normal night's sleep to estimate the effect of sampling (i.e. how many of the new abnormalities detected were the result of obtaining an additional EEG and not necessarily a SD one), the activation rate was 18%, thus identifying SD as the likely precipitant of EEG abnormalities [8]. In another series, 53% (15/29) of patients with definite or probable epilepsy and normal routine EEGs demonstrated IEDs on a subsequent sleep-deprived EEG [9]. Increased IED density was also observed in the EMU after SD in 10 patients with generalized epilepsy [10].

Transcranial magnetic stimulation (TMS) also provides evidence for an association between SD and seizures. TMS delivers electrical stimuli through the scalp, which, when performed over the motor cortex, leads to activation of the target muscle. Parameters of cortical (i.e. motor threshold, MT) and corticospinal (i.e. motor evoked potential, MEP) excitability can be measured by TMS [11]. As a noninvasive diagnostic tool, TMS has been utilized in several studies of sleep deprivation in PWE. In one report, TMS co-registered to EEG was assessed after SD in 10 patients with juvenile myoclonic epilepsy (JME) and 10 normal subjects. In patients with JME, sleep deprivation induced a significant decrease in short latency intracortical inhibition, and an increase in short latency intracortical facilitation, which was associated with increased paroxysmal activity. A significant decrease in the MT was also observed. These changes were not present in normal subjects [12]. In another series, 15 generalized and 15 focal epilepsy patients were compared to 13 normal subjects before and after SD. Both hemispheres in generalized epilepsy patients, and the hemisphere ipsilateral to the seizure focus in focal epilepsy patients, demonstrated increased cortical hyperexcitability after SD, changes which were more prominent in these regions compared to normal subjects [13].

Overall, the literature supports SD as a seizure precipitant, both when measured by qualitative (i.e. patient reported sleep diaries) and quantitative (e.g. EEG, TMS) methods. The mechanism(s) responsible for seizure provocation have not been completely elucidated, but several theories have been posited. For example, SD has consequences on subsequent sleep stages, resulting in rebound phenomena, including an increased percentage of total sleep time in non-rapid eye movement (NREM) sleep stages N2 and N3. This is particularly relevant to seizures, as interictal epileptiform discharges (IEDs) and seizures tend to be more prevalent during particular stages of NREM sleep, depending on the epilepsy syndrome. For example, in a series of 133 patients with focal epilepsy who underwent video EEG monitoring, 264/613 (43%) of captured seizures arose from sleep, with the majority (67%) occurring during N2 [14]. In contrast, the IEDs of generalized epilepsies such as absence epilepsy and juvenile myoclonic epilepsy may demonstrate higher amplitudes and/or increased frequencies during N3 [15]. Thus, the increased proportion of time spent in NREM sleep after SD may contribute to SD provoked epileptogenicity.

The pathophysiology of sleep also provide a scientific rationale for the exacerbation of IEDs and seizures during NREM sleep. Stage N2 is characterized by sleep spindles, a distinct group of waves detected via EEG with a frequency of 11 - 16 Hz (most commonly 12 - 14 Hz) [16]. Spindles are generated by the reticular nucleus of the thalamus, which is composed of GABAergic neurons that possess intrinsic rhythmic activity in spindle-frequency range. The rhythmic spike-bursts produced by the GABAergic thalamic reticular nucleus is relayed to thalamocortical nuclei that generate rhythmic, spindle-frequency inhibitory postsynaptic potentials (IPSPs), which are then transmitted to the cerebral cortex via glutamatergic thalamic afferents, resulting in excitatory postsynaptic potentials (EPSPs) at spindle-frequency in the cortex [17]. Thus, the sleep spindles characteristic of N2 sleep provide synchronous bursts of excitatory input to cortical cells. In focal epilepsy, the addition of spindle-related excitatory input to epileptic neurons, which are already intrinsically hyperexcitable and demonstrate impaired inhibition, can increase the likelihood of IED propagation and subsequent seizures. In contrast, the exacerbation of IEDs in generalized epilepsies may be more related to synchronicity, where the amplitude of temporally and spatially summed EPSPs and IPSPs generate action potentials that underlie the spike component of IEDs [18].

A phasic phenomenon known as cyclic alternating pattern (CAP) also occurs during sleep and may contribute to

SD-provoked seizures. CAP represents an arousal related event, and consists of 2 phases: A and B. Phase A occurs against a microarousal related background, and may be divided into one of three types (graded in order of decreasing synchrony): A1, where synchrony predominates i.e. < 20% of the EEG is desynchronized; A2, composed to admixed slow/fast rhythms and 20 - 50% EEG desynchrony; and A3, where fast, low voltage rhythms predominate and the EEG demonstrates > 50% EEG desynchrony. Phase B of CAP consists of the background level of the sleep stage [19]. Thus, Phase A represents unstable sleep with greater EEG synchrony, and is relatively excitatory compared to Phase B, resulting in IED exacerbation during CAP, particularly during Phase A. Consequently, IED exacerbation during CAP has been reported in several studies of PWE. In focal epilepsies, IEDs in the temporal and frontotemporal regions are increased during Phase A compared to Phase B and non-CAP sleep. In addition, 96% of IEDs occur during CAP Phase A, 91% of secondarily generalized focal bursts occur in CAP overall, and in the temporal region, 83% of seizures recorded in N2 occurred during CAP Phase A. In generalized epilepsies, IEDs also increase during Phase A, with 70% occurring during Phase A1, 24% during Phase A2, and 6% during Phase A3. IEDs may also prolong and increase CAP cycles, resulting in bidirectional excitatory feedback where unstable CAP exacerbates IEDs, and IEDs increase CAP cycles [20].

The role of sleep deprivation as a common seizure precipitant is supported by a preponderance of clinically and objectively measured evidence. The pathophysiology of sleep, and its interplay with IED generation, provides scientific rationale for the provocative nature of sleep deprivation in epileptogenicity. As a preventable seizure precipitant, education regarding sleep deprivation should always be provided to, and assessed in the evaluation of, any patient presenting with seizures.

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