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Sleep in Epilepsy

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ABSTRACT

The relationship between sleep and epilepsy is bidirectional. While certain types of seizures occur almost exclusively during sleep, sleep deprivation can precipitate seizures and can activate interictal epileptiform discharges (IEDs) in the electroencephalogram (EEG). While non-rapid eye movement sleep is an activator of IEDs and seizures, rapid eye movement sleep suppresses them. Nocturnal seizures need to be distinguished from parasomnias. Epileptic seizures and IEDs result in changes of sleep architecture, while antiepileptic drugs have variable effect on sleep and wakefulness. Nearly one-third of patients with epilepsy complain day time somnolence. In addition to nocturnal seizures and antiepileptic drugs (AEDs), associated sleep disorders such as sleep apnoea and restless leg syndromes might be responsible for daytime sleepiness in persons with epilepsy.

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INTRODUCTION

It has been known since antiquity that sleep and epilepsy are intimately related. The relationship between sleep and epilepsy is bidirectional **(Table 1).** Certain types of seizures occur almost exclusively during sleep, and sleep deprivation can precipitate seizures and can activate IEDs in the EEG. While non-rapid eye movement (NREM) sleep is an activator of IEDs and seizures, rapid eye movement (REM) sleep suppresses them **(Table 2).** Nocturnal seizures can mimic parasomnias. Epileptic seizures and IEDs result in changes of sleep architecture, while AEDs affects sleep and wakefulness in different ways.

Effects of sleep on epilepsy :

Interictal epileptiform discharges :

Sleep is a potent activator of IEDs in the EEG. A number of studies have examined the frequency of IEDs in different stages of sleep in patients with temporal lobe epilepsies (1-7). Focal IEDs become more frequent and tend to become bilateral and generalized during sleep (3,5,6). The IEDs are most frequent during stages 3 and 4 NREM sleep and least frequent during REM sleep (4,5). The ability of NREM sleep to activate IEDs appears to be related to the intense neuronal synchronization that occurs between brainstem, thalamus and cortex in this state. The sleep activation of IEDs

Table 1: The bidirectional relationship between sleep and epilepsy

Effects of sleep on epilepsy
▪ Activation of interictal epileptiform discharges (IEDs)
▪ Activation of epileptic seizures
Effects of sleep deprivation
▪ Activation of IEDs
▪ Activation of epileptic seizures
Effects of epilepsy on sleep
▪ Disruption of sleep by IEDs and seizures
Effects of antiepileptic therapy on sleep
▪ Antiepileptic drugs
▪ Vagus nerve stimulation
Effect of sleep disorders on epilepsy
▪ Obstructive sleep apnoea syndrome
▪ Restless leg syndrome
▪ Parasomnias

Table 2: Effect of sleep stages on epilepsy

NREM sleep	REM sleep
Synchronization of EEG	Desynchronization of EEG
Activation of IEDs	Suppression of IEDs
Generalization of focal IEDs	More localized IEDs
Increased likelihood of seizures	Decreased likelihood of seizures

is profound in certain epilepsy syndromes such as benign childhood epilepsy with centro-temporal spikes (benign rolandic epilepsy) (8,9) and in epilepsy with continuous spike and waves during slow-wave sleep (10,11). The essential feature of the latter disorder is a diffuse 2-3 Hz spike-wave discharges occurring throughout NREM sleep and occupying at least 85% of slow-wave sleep (10,11). In children with benign rolandic epilepsy, marked activation of centro-temporal spike discharges occurs during NREM sleep, while awake EEG record may show few or occasionally no IEDs at all (8,9). The capacity of sleep to activate IEDs indicate the importance of obtaining EEG recording during sleep, in addition to wakefulness, in patients with suspected diagnosis of epilepsy.

Epileptic seizures :

As with IEDs, nocturnal focal seizures occur predominantly in NREM sleep and seldom during REM sleep. However, in contrast to IEDs, seizures are more common in stages 1 and 2 rather than in slow-wave sleep (12,13). Partial seizures generalize more often during NREM sleep than wakefulness (12,13).

In patients with nocturnal frontal lobe epilepsy (NFLE), the seizures occur exclusively during sleep. NFLE is often familial, autosomal dominant in inheritance and the gene locus has been mapped to the nicotinic acetylene receptor α4 subunit on chromosome 20 (14). The motor behaviour in nocturnal frontal lobe seizures often mimics parasomnias (15). Furthermore, IEDs are often absent in frontal lobe epilepsies and ictal EEG is usually obscured by muscle artefacts. The brief duration, stereotypy of the spells and lateralizing features would favour epileptic events than parasomnias (15).

In children with benign rolandic epilepsy, the seizures occur almost exclusively during sleep (8,9). The AED treatment is often differed in children with benign rolandic epilepsy because of the infrequent nocturnal occurrence of seizures and the tendency of the disorder to spontaneously remit by adolescence.

Ring chromosome 20 should be suspected in patients with nocturnal frontal lobe nonconvulsive status epilepticus and normal brain magnetic resonance imaging (16). Individuals with ring chromosome 20 syndrome may have

normal cognition despite poorly controlled seizures and no dysmorphic features, making the diagnosis difficult unless there is a high index of suspicion (17).

Effects of epilepsy on sleep :

Interictal epileptiform discharges :

A number of studies have shown that IEDs during sleep unassociated with clinical seizures could disrupt the nocturnal sleep and could contribute to daytime sleepiness (18,19). Suppressing the IEDs during sleep by bedtime benzodiazipine group of AEDs often improves daytime alertness and school performance in selected children with certain epilepsy syndromes such as benign rolandic epilepsy and in epilepsy with continuous spike waves during slow-wave sleep (11,19).

Epileptic seizures :

Both focal and generalized seizures at night cause considerable disruption of sleep (12,13). Compared to patients with epilepsy without nocturnal seizures, in those with nocturnal seizures, the total sleep time decreases and the number of nocturnal awakenings increase (12,13). The most striking change in sleep architecture in patients with nocturnal seizures is an absolute and relative reduction in REM sleep. Patients with drug-resistant nocturnal generalized seizures are more prone to sudden unexpected death in epilepsy (20).

Antiepileptic drugs :

The AEDs in general improves sleep efficiency by decreasing sleep latency and nocturnal awakenings (21,22). An exception is phenytoin, which increases awakenings and decreases sleep efficiency. Phenobarbitone, carbamazepine and benzodiazipines decrease REM sleep whereas gabapentin and lamotrigine enhance REM sleep. Most of the AEDs cause daytime sleepiness; however, felbamate and lamotrigine can result in insomnia. Benzodiazipines and phenobarbitone can aggravate obstructive sleep apnoea (OSAS) syndrome. The OSAS can also be worsened by vagus nerve stimulation used to treat certain AED-resistant epilepsies (23).

Daytime sleepiness and epilepsy :

Nearly one-third of patients with epilepsy show elevated scores on the Epworth Sleepiness Scale (18). The factors that contribute to day time somnolence in persons with epilepsy are listed in **Table 3.** It should be remembered that associated sleep disorders such as OSAS and restless leg syndrome might be responsible for daytime somnolence in persons with epilepsy. Additionally, OSAS may increase the frequency of seizures by producing sleep deprivation or by inducing hypoxemia, and treatment of OSAS can improve seizure control.

Table 3: Causes of daytime sleepiness in persons with epilepsy

Antiepileptic drugs
Nocturnal seizures
Associated sleep disorders
▪ Obstructive sleep apnoea syndrome
▪ Restless leg syndrome

Sleep deprivation and epilepsy :

Sleep deprivation can aggravate IEDs and seizures. Sleep deprivation is widely used in EEG laboratories and epilepsy monitoring units as a method of inducing IEDs and seizures (24). The influence of sleep deprivation in precipitating seizures is most evident in patients with juvenile myoclonic epilepsy. Patients with this disorder exhibit myoclonic jerks of the upper limbs and generalized tonic-clonic seizures usually within one hour after awakening in the morning, especially following sleep deprivation (25).

Evaluation of the patient with nocturnal spells :

The differential diagnosis of nocturnal events, especially between NFLE and parasomnias can be very difficult. More than one-third of patients with NFLE present with personal or family history of parasomnias, thereby complicating the differential diagnosis between these two disorders (15). An Australian group of researchers demonstrated that clinical history alone can accurately discriminate between NFLE and parasomnias (26). In the test battery they developed, called FLEP scale, later age at onset, longer duration (>2 minutes) of events and occurrence during later part of sleep favored parasomnia, while stereotypy, clustering and ability to recall were more frequently associated with NFLE (26). A recent study that compared the diagnostic value of FLEP scale against nocturnal polysomnography showed that FLEP scale failed to give a diagnosis of NFLE in only 4 out of 71 (5.6%) patients (27).

The correct characterization of nocturnal spells requires collaboration between an epileptologist and a sleep specialist. When the spells also occur during wakefulness, especially if the interictal EEG is abnormal, the diagnosis of epilepsy is usually straightforward. When the spells occur only during sleep and the clinician suspects that seizures are more likely than parasomnias, an awake and sleep EEG, often preceded by sleep deprivation, often settles the diagnosis. The brief and stereotypic nature of the nocturnal spells favour epilepsy (26,27). If the interictal EEG is normal, prolonged recording to capture the spells in an epilepsy monitoring unit (EMU) become necessary. If parasominas are more likely than seizures, poysomonography with full

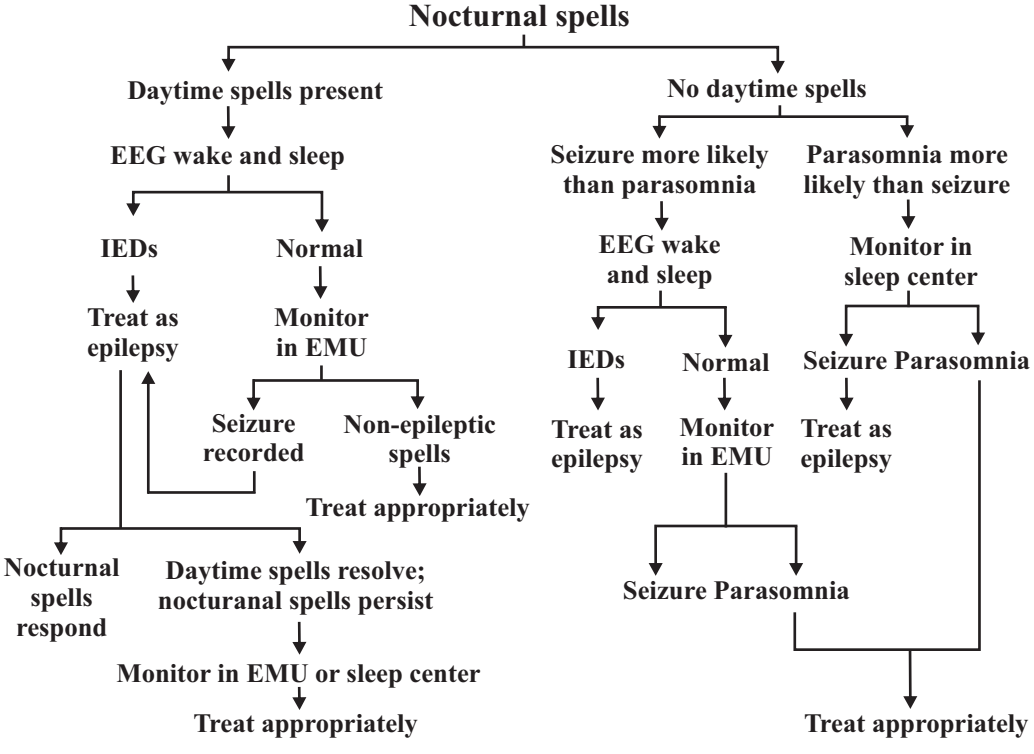

FIGURE 1 : Algorithm for evaluation of patients with nocturnal spells

EEG montage will be a better option. An algorithm for the evaluation of a patient with nocturnal spells is illustrated in **Figure 1.**

REFERENCES

1. Klass DW (1975). Electroencephalographic manifestations of complex partial seizures. *Adv Neurol* **11**:113-140.
2. Autret A, Laffont F, Roux S (1983). Influence of waking and sleep stages on the interictal paroxysmal activity in partial epilepsy with complex partial seizures. *Electroencephalogr Clin Neurophysiol* **55**:406-410.
3. Summarintano M, Gigli GL, Gotman J (1991). Interictal spiking during wakefulness and sleep and localization of foci in temporal lobe epilepsy. *Neurology* **41**:290-291.
4. Malow BA, Kushwaha R, Lin X, Morton R, Aldrich M (1997). Relationship of interictal epileptiform discharges to sleep depth in partial epilepsy.

Electroencephalogr Clin Neurophysiol **102**:20-26.

5. Malow BA, Lin X, Kushwaha R, Aldrich MS (1998). Interictal spiking increases with sleep depth in temporal lobe epilepsy. *Epilepsia* **39**:1309-1316.
6. Malow BA, Selwa LM, Ross D, Aldrich MS (1999). Lateralizing value of interictal spikes on overnight sleep-EEG studies in temporal lobe epilepsy. *Epilepsia* **40**:1587-1592.
7. Sylaja PN, Radhakrishnan K (2001). The role of scalp EEG in the presurgical evaluation of patients with medically refractory temporal lobe epilepsy. *Am J END Technol* **41**:116-135.
8. Guerrini R, Pellacani S (2012). Benign childhood focal epilepsies. *Epilepsia* **53 (Suppl. 4)**: 9-18.
9. Samaitienè R, Norkūnienè J, Tumienè B, Grikinienè J (2013). Sleep and behavioural problems in rolandic epilepsy. *Pediatr Neurol* **48**:115-122.
10. Jayakar PB, Seshia SS (1991). Electrical status epilepticus during slow-wave sleep: a review. *J Clin Neurophysiol* **8**: 299-311.
11. Kramer U, Saqi L, Goldberg-Stern H, Zelnik N, Nissenkorn A, Ben-Zeer B (2009). Clinical spectrum and medical treatment of children with electrical status epilepticus in sleep (ESES). *Epilepsia* **50**:1517-1524.
12. Bazil CW, Walczak TS (1997). Effects of sleep and sleep stage on epileptic and nonepileptic seizures. *Epilepsia* **38**:56-62.
13. Minecan D, Natarajan A, Marzec M, Malow B (2002). Relationship of epileptic seizures to sleep stage and sleep depth. *Sleep* **25**:899-904.
14. Phillips HA, Scheffer IE, Berkovic SF, Hollway GE, Sutherland GR, Mulley JC (1995). Localization of a gene for autosomal dominant nocturnal frontal lobe epilepsy to chromosome 20q13.2. *Nat Genet* **10**:117-118.
15. Provini F, Plazzi G, Tinuper P, Vandi S, Luqaresi E, Montaqua P (1999). Nocturnal frontal lobe epilepsy. A clinical and polygraphic review of 100 consecutive cases. *Brain* **122**:1017-1031.
16. Inoue Y, Fujiwara T, Matsuda K et al. (1997). Ring chromosome 20 and nonconvulsive status epilepticus. A new epileptic syndrome. *Brain* **120**:939-953.
17. Radhakrishnan A, Menon RN, Hariharan S, Radhakrishnan K (2012). The evolving electroclinical syndrome of "epilepsy with ring chromosome 20". *Seizure* **21**:92-97.

18. Malow BA, Bowes RJ, Lin X (1997). Predictors of sleepiness in epilepsy patients. *Sleep* **20**:1105-1110.

19. Can S, Baldeweg T, Cross JH (2011). A role for sleep disruption in cognitive impairment in children with sleep. *Epilepsy Behav* **20**:435-440.

20. Ryvlin P, Nashef L, Tomson T (2013). Prevention of sudden unexpected death in epilepsy: a realistic goal. *Epilepsia* **54 (Suppl 2):**23-28.

21. Sammaritano M, Sherwin A (2000). Effect of anticonvulsants on sleep. *Neurology* **54 (Suppl. 1)**:S16-S24.

22. Placidi F, Scalise A, Marcianai MG, Romogi A, Diomedi M, Gigli GL (2000). Effect of antiepileptic drugs on sleep. *Clin Neurophysiol* **111 (Suppl. 2):** S115-S119.

23. Malow BA, Edward SJ, Marzec M, Sagher O, Fromes G (2000). Effects of vagus nerve stimulation on respiration during sleep: a pilot study. *Neurology* **55**: 1450-1454.

24. Radhakrishnan K, Satoshkumar B, Venugopal A (1999). Pravalence of benign epileptiform variants observed in an EEG laboratory from South India. *Clin Neurophysiol* **110**:280-285.

25. Vijai J, Cherian PJ, Sylaja PN, Anand A, Radhakrishnan K (2003). Clinical characteristics of a South Indian cohort of juvenile myoclonic epilepsy probands. *Seizure* **12**:490-496.

26. Derry CP, Davey M, Johns M et al. (2006). Distinguishing sleep disorders from seizures. Diagnosing bumps in the night. *Arch Neurol* **63**:705-709.

27. Manni R, Terzaghi M, Repetto A (2008). The FLEP scale in diagnosing nocturnal frontal lobe epilepsy, NREM and REM parasomnias: data from a tertiary sleep and epilepsy unit. *Epilepsia* **49**:1581-1585.