SLEEP DISORDERS IN ADULTS WITH EPILEPSY

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Effects of sleep on epilepsy

- Non-rapid eye movement (NREM): state of EEG synchronization, relative preservation of muscle tone
  - Intra-epileptiform (IED) discharges are activated (most occur during N1 and N2 stage)
  - Spike frequency increases with increasing depth of sleep
  - Perpetuated by hypersynchrony of neuronal networks
  - More diffuse discharges

- Rapid eye movement (REM): desynchronization of EEG, skeletal muscle atonia
  - Spike frequency decreases
  - Restricted field of discharges (used to identify focus of seizures)

- Adenosine
  - Decreases in sleep
EPILEPSY AND SLEEP

Sleep architecture in Epilepsy

- Reduced REM sleep time
- Prolonged REM latency
- Increased wake after sleep onset (WASO)
  - Reduced total sleep time and sleep efficiency
  - Increased number of arousals, awakenings, and stage shifts
- Sleep macroarchitecture in some patients is normal, or normalizes after treatment
- Abnormalities in sleep architecture is more likely in temporal lobe epilepsy (TLE) compared to idiopathic generalized epilepsies (IGE)
Some epilepsy syndromes occur primarily in sleep or upon awakening.

A large prospective study found 7.5% of 1,200 patients had seizures restricted to sleep:

- If a patient has SZs only during sleep > 2 years, unlikely to have a SZ awake (and could drive a motor vehicle even if not SZ-free);
- Only 11% of people with sleep-related SZs developed seizures when awake, typically within 2 years of the first nocturnal SZ;
- Diurnal SZs in them were often triggered by sudden withdrawal of antiepileptic medication (AED);

**Awakening**

- Primary generalized seizures upon awakening
- Juvenile Myoclonic Epilepsy

**NREM sleep**

- Nocturnal Frontal Lobe Epilepsy
- Benign focal epilepsy of childhood with centrotemporal spikes
- Lennox Gastaut syndrome (tonic seizures)
- Panayiotopoulos syndrome
- Electrical status epilepticus during sleep and Landau-Kleffner syndrome

“State-dependent” Epilepsies

D’Alessandro, Guarino et al. 2004
EPILEPSY AND SLEEP

Timing seizure types and epilepsy syndromes

- **Sleep:** Tonic-clonic seizures, tonic, automotor, frontal and parietal seizures
- **Wakefulness:** Absence, atonic, myoclonic seizures, myoclonic, epileptic spasms
- Peak frequency of epilepsies vary with circadian rhythm
- Seizure occurrence correlates with dim light melatonin secretion
EPILEPSY AND SLEEP

Patients with IGE (especially JME) are more likely to have seizures on waking.

Patients with mesial TLE are more likely to have seizures during wakefulness.

Patients with extra-TLE are more likely to have seizures on in sleep.

Patients with FLE are more likely to have seizures in sleep, specifically in NREM stages.

Patients with IGE often have IEDs in wakefulness and sleep, but often increase through sleep stages and decrease in REM.

Patients with Focal epilepsy often have IEDs that increase through sleep stages and decrease substantially in REM.

SLEEP DEPRIVATION AND EPILEPSY

- Seizure precipitant (especially in awakening epilepsies)
- Triggering factor for seizures in 71% of cases in recent study of 104 patients
- Can induce IEDs
- Sleep deprivation EEG protocol
- Juvenile Myoclonic Epilepsy
<table>
<thead>
<tr>
<th>AED</th>
<th>Sleep Disorders</th>
<th>Sleep Architecture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive Effects</td>
<td>Negative Effects</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Insomnia</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Insomnia, Willis Ekbomb disease, REM sleep disorder</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Willis Ekbomb disease</td>
<td>None</td>
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<tr>
<td>Valproate</td>
<td>Willis Ekbomb disease</td>
<td>Obstructive sleep apnea</td>
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<tr>
<td>Gabapentin</td>
<td>Willis Ekbomb disease, insomnia</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Consolidating sleep reducing arousals stage shifts</td>
<td>Insomnia, REM sleep behavior disorder</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Willis Ekbomb disease (case reports)</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Willis Ekbomb disease, insomnia, daytime attention</td>
<td>Obstructive sleep apnea</td>
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<tr>
<td>Topiramate</td>
<td>Weight loss, Obstructive sleep apnea</td>
<td>Willis Ekbomb disease</td>
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<tr>
<td>Zonisamide</td>
<td>Obstructive sleep apnea</td>
<td>Willis Ekbomb disease</td>
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</table>
SEIZURE DISORDERS DURING SLEEP

- Nocturnal Temporal Lobe Epilepsy
- Benign Epilepsy of Childhood with Centro-temporal Spikes
- Nocturnal Paroxysmal Dystonia
- Nocturnal Frontal Lobe Epilepsy
- Autosomal Dominant Frontal Lobe Epilepsy
## CHARACTERISTICS OF NOCTURNAL EVENTS

<table>
<thead>
<tr>
<th>Feature</th>
<th>Disorders of Arousal</th>
<th>REM Sleep Behavior Disorder</th>
<th>Nocturnal Seizures</th>
<th>Psychiatric Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of night</td>
<td>First third to half of night</td>
<td>Latter half of sleep period during REM</td>
<td>Sporadic</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Eye opening</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Stereotypic movements</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Memory</td>
<td>Partial or no memory</td>
<td>Vivid dream recall</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Duration</td>
<td>Minutes</td>
<td>Seconds to minute</td>
<td>Minutes</td>
<td>Minutes to hours</td>
</tr>
<tr>
<td>Frequency</td>
<td>Typically 1 or less per night</td>
<td>Nightly events during REM</td>
<td>Sporadic to multiple per night</td>
<td>Sporadic</td>
</tr>
<tr>
<td>PSG findings</td>
<td>Arousal from slow-wave sleep</td>
<td>Excessive electromyography tone in REM</td>
<td>Epileptiform activity</td>
<td>Wake state before the event</td>
</tr>
</tbody>
</table>
Prevalence of primary sleep disorders in epilepsy
Primary sleep disorders are 2-3 times more common in adults with epilepsy compared to age-matched controls in the general population:
- Especially when seizures are poorly controlled and/or
- Complicated by comorbid neurological conditions.

Most common sleep disorders in people with epilepsy:
- Sleep maintenance insomnia
- Excessive daytime sleepiness (EDS)
- Obstructive sleep apnea (OSA)

Adults with epilepsy who complain of sleep problems have lower quality of life (QOL) compared to those with epilepsy but no sleep complaints.

SLEEP MAINTENANCE INSOMNIA

Most common sleep complaint in adults with epilepsy

- **51%** of 152 patients with epilepsy (mean age 46 years) reported moderate to severe insomnia
- **72%** rated themselves as “poor sleepers”
- Poorer sleep quality and more severe insomnia correlated with:
  - Higher numbers of antiepileptic medications (AEDs); and
  - Were significant predictors of lower quality of life (QOL).

Etiology of sleep disruption in epilepsy:

- Inadequate sleep hygiene
- Coexisting sleep disorders
- Nocturnal seizures
- Effect of antiepileptic drugs
ALGORITHM FOR EVALUATION OF INSOMNIA IN EPILEPSY

1. Prior Sleep History, Current Sleep trial, psychiatric evaluation, sleep medication, history of sleep disturbances.
   - Yes
   - No
   - Positive: Waking affective disorder
   - No
   - Optimize medication and discontinuation of sleep medications.
   - Yes
     - Consider polysomnography and treatment with sleep medication.
     - No
     - Positive: Treatment with sleep medication.

2. Still having insomnia?
   - Yes
   - Polysomnography with portable extended EEG recording.
   - Negative findings
   - Positive findings
   - Positive: REM without Arousal Syndrome (WASM)
   - Sleep Disorder: Non-rapid Eye Movement Sleep Behavior Disorder
   - Sleep Disorder: Sleep-related breathing disorder
   - Narcolepsy: Increased nocturnal sleepiness and sleep fragmentation
   - Periodic Limb Movements associated with insomnia
   - NEEM: Narcolepsy-Associated Hypocretin Deficiency
   - Consider behavioral therapy, review sleep hygiene, consider treatment.

3. No
   - Treat with sleep medication.
EXCESSIVE DAYTIME SLEEPINESS

Second most common sleep complaint in adults with epilepsy

- **48%** of 99 unselected patients with epilepsy complained of EDS (Epworth Sleepiness Score of > 11)
  - Anxiety (and to lesser extent neck circumference) correlated with EDS
- **20%** of 117 people with epilepsy complained of EDS vs. **7%** of 30 healthy volunteer
  - Poor seizure control was the strongest independent risk factor for poor sleep quality (odds ratio [OR] = 2.4)
EVALUATION OF HYPERSOMNIA IN EPILEPSY

- Poor sleep hygiene, altered sleep schedule or sleep deprivation
  - Yes: Review sleep hygiene, improve schedule and cleanliness, and sleep habits
  - No: Possible snoring or witnessed episodes, excessive movements or increased awakenings during sleep
    - Yes: Polysomnogram with possible extended EEG recording and possible MSLT
    - No: Optimize medication dose and timing to avoid daytime sedation
  - Still sleepy: Proceed with MSLT to rule out disorder of hypersomnia
  - Positive study
  - Negative study

- REM without atonia — screen for REM sleep behavior disorder
- Sleep disordered breathing — treat with CPAP or appliance, etc.
- Nocturnal seizures, increased interictal activity or sleep fragmentation — optimize AEDs
- Periodic limb movements associated with aroused — treat potentially with gabapentinoid medications
- NREM parasomnia—consider behavioral therapies, review sleep hygiene and consider treatment
OBSTRUCTIVE SLEEP APNEA IN ADULTS WITH EPILEPSY

Prevalence of OSA in patients with epilepsy

Meta-analysis by Zhang Lin et al in 2016:

- Prevalence of mild-to-severe OSA (AHI or RDI >5) in people with epilepsy was 33.4% (95% CI 20.8–46.1%) compared to 21.2 % of general population in USA
  - Mild-to-severe OSA in males with epilepsy is 44.8% compared to 27.5 % in general population
  - Mild-to-severe OSA in females with epilepsy is 25.5% compared to 12.4% in general population
- Prevalence of moderate-to-severe OSA (AHI or RDI >15) in people with epilepsy was 9.7 % (95 % CI 5.1–14.4 %)
- Patients with refractory epilepsy are not more susceptible to OSA compared to those with controlled epilepsy (OR 1.66; CI1.22-2.27 P=0.43.)
OSA Risk factors and comorbidities

- **Males**
- **Overweight or obese**
- African-Americans
- Post-menopausal women
- Family history
- **Large neck size**
- Alcohol or tobacco use
- **Middle age**
- Stroke
- Medically refractory **hypertension**
- Atrial fibrillation

Risk factors that are highlighted are found to be risk factors for OSA in adults with epilepsy
Proposed mechanisms for seizure facilitation in OSA

- Sleep deprivation from frequent arousals increases neuronal excitability
- Frequent arousals or stage shifts
- Intermittent hypoxia $\rightarrow$ oxidative stress $\rightarrow$ activation of inflammatory pathways $\rightarrow$ IL6 and TNF alpha
- Decreased cerebral blood flow
OBSTRUCTIVE SLEEP APNEA IN ADULTS WITH EPILEPSY

- CPAP treatment in people with epilepsy and OSA:
- Higher seizure-free rate (OR 4.03; 95 % CI 1.15 –14.1; P = 0.01).
- Increase in successful outcomes as compared to the untreated patients (OR 5.26; 95 % CI 2.04–13.5; P < 0.001).
Vagal nerve stimulation effect on respiration

- Used for medically refractory focal epilepsy
- Prevalence of OSA is 43.1% compared to 33.4% in all patients with epilepsy
- Decreases REM sleep
- Increases awakenings, wake after sleep onset, NREM 1 sleep stage
PARASOMNIA AND EPILEPSY

- NREM disorders of arousal
- Sleep related bruxism
- Nocturnal Frontal Lobe Epilepsy
Sleep and epilepsy are common but are bad Bed Fellows
Sleep and epilepsy have complex bidirectional relationship
Sleep maintenance insomnia is most common complaint in adults with epilepsy
Excessive daytime sleepiness is second most common complaint
Adults with epilepsy are at increased risk for OSA
QUESTIONS
REFERENCES


