Sleep and Epilepsy

신원철
경희의대 신경과
EEG Findings of sleep and waking state

- Desynchronization
  - Waking
  - REM sleep

- Synchronization
  - NREM sleep
Thalamocortical circuit
Thalamus and epilepsy

- Reciprocal connectivity with cortex
- Efferent cortical inputs to reticular Nu.
- Reciprocal connectivity with the reticular Nu.

- Activation of thalamus during partial epilepsies (Chugani ,94)
- Thalamic lesions in experimental models suppress seizure activity (Modragon and Lamarche, 90)

- General effects on cortical excitability mediated by diffuse projecting such as the anterior and intralaminar thalamic Nu.
Nocturnal seizure: 7.5-45%

Epilepsy syndromes a/c sleep-related seizures

<table>
<thead>
<tr>
<th>Epilepsy syndrome</th>
<th>Age of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLE</td>
<td>Late childhood to early adulthood</td>
</tr>
<tr>
<td>FLE</td>
<td>Late childhood to early adulthood</td>
</tr>
<tr>
<td>BRE</td>
<td>3-13Y (peak 9-10Y)</td>
</tr>
<tr>
<td>Epilepsy with GTCS on awakening</td>
<td>6-25Y (peak 11-15Y)</td>
</tr>
<tr>
<td>JME</td>
<td>12-18Y (peak 14Y)</td>
</tr>
<tr>
<td>Absence epilepsy</td>
<td>3-12Y (peak 6-7Y)</td>
</tr>
<tr>
<td>Lennox-Gastaut syndrome</td>
<td>1-8Y (peak 3-5Y)</td>
</tr>
<tr>
<td>Continuous spike and slow wave discharges during sleep</td>
<td>8 mo – 11.5Y</td>
</tr>
</tbody>
</table>
IED and Sleep

**NREM sleep**
- As NREM Sleep deepens, IED are activated in partial epilepsies; 34 of 40 TLE - maximal spike rate in SWS *samaritan, et al. 1991*

**REM sleep**
- REM suppress IED
- IED: less frequent than NREM sleep (*Rossi, et al. 1984*)
- If present, more accurate in localizing epileptic foci (*Sammaritano, et al. 1991; malow, et al. 2000*)

**Three factors for state-dependence of IEDs**
- Subcortical-cortical interplay and EEG synchronization
- Cortical excitability
- Location of epileptic lesion
NREM Effects on IED and Seizures

- IN ED: in NREM > REM

- Neuronal synchronization within thalamocortic networks during NREM sleep
  - enhanced neuronal excitability
  - more diffuse distribution of focal discharges and facilitation of seizure and IN ED in partial epilepsy

- Neuronal synchronization is disrupted on arousal or transition to REM sleep, focal discharges become more localized.

- Varying levels of hyperpolarization of TC preferentially activates IED or seizure by different levels of sleep depth
Generalized epilepsies

• Primary generalized tonic clonic seizure
  - Exclusively nocturnal seizure only in 8 %
  - ↑ in NREM sleep, ↓ in REM sleep

• Absence seizure
  - Difficult to diagnose
  - Fluttering of eyelids
  - ↑ in NREM sleep, absent in REM sleep

• Juvenile myoclonic epilepsy
  - Occurs shortly after awakening
  - ↑ at sleep onset and on awakening (esp. when induced)
Generalized epilepsies

• **Lennox-Gastaut syndrome**
  - Tonic seizure activated by sleep
  - Typically slow spike and wave, ↑ in NREM sleep
  - In sleep, intermixed with trains of fast spikes of 10-25 Hz lasting 2-10 sec (grand mal discharges)
  - Sometimes, burst-suppression-like pattern

• **West syndrome**
  - Maximal on arousal from sleep or before going to bed
  - ↑ hypsarrhythmia in NREM sleep
  - Burst-suppression pattern
  - May be normalized during REM sleep
Partial epilepsies

- More frequent during the day
- ↑ in NREM sleep

- BRE
  - Seen mostly during drowsiness and sleep
  - IIDTs in all stages of sleep
Relationship of Epileptic seizures to Sleep

- NERM activates seizures and IED.
- REM suppresses seizures and IED.
- IED is accentuated in deep stages of NREM.
- Seizures are prominent in lighter stages of NREM.
Sleep complaints in epileptic patients

◆ Excessive daytime sleepiness (EDS), fatigue or disrupted sleep; in 30-37% of patients; Effects of AED or Seizures or primary sleep disorder?

◆ Poor sleep hygiene in epileptic patients
  ▪ 30% of patients (Manni 98)
  ▪ More common males and younger
  ▪ Less likely to have daytime sleepiness
  ▪ More likely to have daytime sleepiness

◆ Early awakening, frequent nocturnal awakening, difficulty initiating sleep
  : partial Sz and poorer Sz control> gen Sz (Abad-Alegria, 97)
Daytime sleepiness and disrupted sleep

◆ 11-28% of epileptic patients: ESS > 10
  
  (Malow 97, Manni 98, Armaganijan 2000)
  
  - sleep apnea & Restless leg syndrome in epileptic patients

◆ Relation with number of AED, seizure frequency?
  
  - no relation ESS with AED number and Sz frequency control
    Malow(97), Manni(98)
  
  - significant correlation between ESS and number or AED & Sz control
    Sanchez del Leon, 97
Sleep architecture in epileptic patients

- Disrupted sleep in epileptic patients with seizure-free night
  - Increased latency to sleep onset
  - Increased number and duration of awakenings
  - Increase in the number of shift between sleep stages
  - Increased stages 1 & 2 sleep
  - Decreased sleep efficacy
  - Decrease in total sleep time
  - Reduction of REM sleep time
  - Reduction in the density of sleep spindles and K-complex
  - Increase in sleep onset latency and REM latency

- AED effect or epilepsy effect?
Effect of Epilepsy on Sleep

◆ more prominent sleep abnormalities (*Touchon et al.*, 91)
  ▪ Patients with Gen seizure & those with frequent seizure
  ▪ medically intractable seizure

◆ Recently diagnosed patients; greater sleep instability & fragmentation
  ; Marked increase of awaking, decreased SE in TLE patients < 3 Mo duration

◆ Single Gen seizure; increase REM latency, decrease or fragment amount of REM sleep
Effect of Epilepsy on Sleep

- Seizure type and sleep
  - ↑ WASO and sleep fragmentation in all types of epilepsy.
  - ↓ NREM sleep stages 1 and 2 and REM sleep in generalized seizures.
  - ↓ REM only without rebound in CPS
- The more severe the seizure is, the more extensive the sleep deficit is.
- Kindling causes sleep disorders in addition to seizures. --> permanent change in sleep physiology in epilepsy
Generalized seizure effect on sleep

- Patients with generalized seizures have more frequent sleep abnormalities than those with partial simple or partial complex epilepsy

- With recurrent Gen. Seizure during sleep (*Besset, 82, Touchon, 91*)
  - Decrease in TST (14%)
  - Increase in WASO (63.9%)
  - Increased duration of awakening
  - 50% decrease in REM sleep
  - With no REM rebound on the following nights
  - 24% increase in stage 1 and 2 of NREM sleep
  - No notable change in S3 & S4
  - Decrease in the number of sleep spindles & K-complexes or an intermixing of spike discharge with K-complexes

- Without Gen. Seizure during sleep (*Touchon et al. 91*)
  - Normal NREM and REM latency
  - Sleep instability of increased number of stage shift and increased number an duration of awakening
Partial seizure effect on sleep

- No any marked changes in sleep latency, TST, REM latency, amount NREM

- Increase in SE, increase number of stage shift in epileptic patients, regardless of whether they had seizure during sleep

- Specific reduction in S3 & S4 of NREM sleep in neocortical focus seizure (*Montplaisir et al, 1985*)

- More severe sleep disturbance in patients with TLE compared with extratemporal lobe epilepsy (*Sammaritano & Saint Hilaire, 97*)
Fig. 1. Example of a sleep histogram of a FLE patient.

Fig. 2. Example of a sleep histogram of a TLE patient.
Effect of AED on sleep

◆ Vigilance impairment and sleep disorganization in TLE were corrected after 1 month of CBZ Tx *(Touchon, 87)*

◆ AED can affect sleep and seizures
  - Normalization and stabilization of sleep
    ; Result of to suppression of seizures
    ; Sleep stabilizing effect
  - Improvement of seizure control by stabilizing sleep

◆ AED effect to sleep architecture
  - Restoration of sleep stability in successfully treated patients ; decreased in time spent awake during sleep cycle after use of AED *(Declercke, 91)*
  - Delay REM onset or decrease the percent of time spent in REM sleep
## Summary of AED effects on sleep

<table>
<thead>
<tr>
<th>AED</th>
<th>Sleep latency</th>
<th>Sleep efficacy</th>
<th>Stage I</th>
<th>SWS</th>
<th>REM</th>
<th>Daytime drowsiness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturate</td>
<td>+</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>+</td>
<td>NE</td>
<td>NE</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Carbamazepine</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>+</td>
<td>NE</td>
<td>-</td>
<td>NE</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>NE</td>
<td>NE</td>
<td>-</td>
<td>NE</td>
<td>NE</td>
<td>-</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>+</td>
<td>+/NE</td>
<td>?</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>-/NE</td>
<td>+/NE</td>
<td>?</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>?</td>
<td>?</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>?</td>
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<tr>
<td>Tiagabine</td>
<td>NE</td>
<td>+</td>
<td>NE</td>
<td>+</td>
<td>NE</td>
<td>?</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>-/NE</td>
</tr>
</tbody>
</table>
Lamotrigine

- Increase in percentage of REM sleep (8.5–13.6%)
- Decrease in fragmentation of REM sleep
- Reduction in the number of spike discharges
- No correlation between the increase in REM sleep & decrease in spikes

*Placidi et al (2000)*
Carbamazepine

Improvement sleep stability & sleep continuity

- Increase in sleep time
- Decreased sleep latency
- Decrease in sleep fragmentation
- Increase in S3 and S4
- Decrease in REM sleep density
- Unchanged REM latency & percentage of REM sleep
- Shortening of first sleep cycle
- Shortening of latency to sleep onset
Phenytoin

- Decrease in SE, decrease in SL
- Increase in S1 and S2
- Small decrease in REM sleep
- Increase or no effect on S3 and S4
- Increase in wakefulness and arousals
Effect or AED on sleep

Valproate

- **No notable alteration of sleep**
  - Mild increase in S3 & S4
  - more frequent arousal
  - no change in percent of REM sleep or TST

- **Stabilization of sleep cycles**
  - Organization of sleep tended to be more regular and the distribution of REM stage over the course of the night was more normal
  - Little or no effect on sleep structure with therapeutic dose

- **Others changes**
  increase in S3 and S4, more frequent arousal, no change in TST
Phenobarbital

- **In acute Tx**
  - Increase in TST with short-term therapy with change with chronic therapy

- **Chronic Tx**
  - Decrease in sleep latency
  - Increase in S1 & S2, sleep spindles
  - Decrease in REM sleep percentage (dose-dependent)
  - Decrease in number and duration of REM cycles
  - Decrease in movement–related arousals
  - Decreased number of arousal and WASO
  - No change in S3,S4
Clonazepam

- Decrease in sleep efficiency
- Decrease in sleep latency
- Decrease in S1
- Decrease in S2
- Decrease in S3 and S4
- Increase REM latency
- Decrease in WASO
- Decrease in arousals
- Increase in spindle density or spindle rate per minute
Effect or AED on sleep

Ethosuximide

- Increase in S1
- Decrease in S3 and S4
- Increase in REM sleep in early cycles & decrease in later cycles
- Increase in number of awakening
- Increase in REM sleep percentage
Effect of AED on sleep

**Gabapentin**

- Increasing S3 and S4 (Rao et al, 88)
- Subjective improvement in nighttime sleep and daytime alertness (Ehrenberg et al, 2000)
- Significant increase in REM sleep percentage, prolonged duration of REM period, decreased number of awakening (Placidi et al, 97)
- No improvement in seizure frequency and IEDs per minute after Tx (Placidi et al, 2000)
Effect of AEDs on Sleep in Epileptics

- DPH: ↓ SL
- CBZ: ? ↓ SL, ? ↑ TST
- VPA: No SL change, ↑ TST, ↓ No. of waking
- PB: ↓ SL, ↓ No. of waking, ↑ TST
- PMD: ↓ SL
- Ethosuximide: ↑ stage 1
- No data on the new AEDs