Effects of Sleep and Circadian Rhythms on Epilepsy

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Agenda

- Effects of sleep stage on seizures and EEG abnormalities
- Circadian physiology – overview
- Distinction of sleep-dependent and circadian-dependent mechanisms that regulate physiological functions
- Effect of circadian rhythms on seizures
Sleep effects on epilepsy
Epilepsy syndromes with a characteristic nocturnal pattern

- Benign Rolandic epilepsy (BECT)
- Autosomal dominant nocturnal frontal lobe epilepsy
- Electrical Status Epilepticus in Sleep (ESES)
- Generalized tonic-clonic seizures on awakening
- Morning myoclonus (JME)
- Paroxysmal nocturnal dystonia
- Supplementary motor area seizures
Distribution of focal seizures across different sleep stages

- Pattern noted from antiquity (1881)
- Contemporary studies in inpatient epilepsy monitoring units
  - Performed on patients with many seizures that persist despite treatment, with the goal to identify seizure focus (consideration of surgery)
  - Cause for epilepsy vary (heterotopia, mesial temporal sclerosis, vascular malformations, etc.)
- Recurrent trends in results:
  - Seizure distribution depends on seizure focus
  - Temporal lobe seizures mid/late afternoon, wake
  - Frontal lobe seizures – night, sleep
  - Fewest seizures observed in REM sleep
Sleep stage – review

• Review from 42 studies (conventional and intracranial), total 1458 patients
• Least number of seizures - in REM compared to all other states
• Compared to REM, in wakefulness
  – 7.83 times more focal seizures,
  – 3.25 times more generalized seizures,
  – Fewer focal discharges
• The highest proportion of seizures occurs in NREM (N2>N1) sleep

Ng and Pavlova, 2013 – in press
Raw Sum of Focal Seizures

Ng and Pavlova, 2013 – in press
<table>
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*Ng and Pavlova, 2013 – in press*
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*Ng and Pavlova, 2013 – in press*
What is so special about REM sleep?

• REM physiology
  – Cerebral blood flow, oxygen demand are increased
  – Irregular respirations, heart rate
  – Reduced network connectivity (from fMRI studies)
  – EEG - desynchrony
  – Motor out put is actively inhibited

• NREM physiology
  – Decreased oxygen demand
  – Regular respirations, heart rate
  – EEG - synchrony
Effects of seizures on sleep

- Sleep fragmentation (Tachibana et al. 1996)
- Decreased amount of REM sleep in epilepsy patients (Besset 1982, Baldy-Moulinier 1982)
- Anticonvulsants may also affect sleep (Bazil et al. 2000)
Effect of seizures on sleep

Tachibana et al 1996

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Effect of sleep deprivation on seizures

- Sleep loss is frequently reported as a factor that provokes seizures in epilepsy patients
- EEG can become abnormal after sleep deprivation
- Sleep deprivation is often used in LTM units to facilitate recording of seizures
- Sleep fragmenting disorders may worsen seizure control
- Anecdotal reports suggests that treatment of even mild OSA may improve seizure control
OSA and epilepsy

• Malow et al, (2000, Neurology) 1/3 of 39 patients with medically refractory epilepsy had RDI≥5
• Chihorek et al (2007) older adults with new or poorly controlled seizures have more frequent OSA
• Malow et al - pilot trial of PAP to help seizure control: 35 of 45 epilepsy patients with PSG had OSA, of them the 32% treated with therapeutic CPAP had a 50% or greater reduction in seizures than those receiving sham CPAP (15%).
Circadian rhythms and epilepsy
Clinically observed day-night variation in... 

- Cognitive function – sundowning
- Movements – RLS
- Neuropathic pain
Day- night variations in focal seizures

- Patients – inpatients monitored for diagnosis or pre-surgical evaluation
- Monitoring – continuous video-EEG
- Result: 50% of all temporal lobe seizures occurred between 3 p.m. and 7 p.m

Pavlova et al, Epilepsy and Behavior, 5 (2004), 44-49
Distribution of Temporal lobe Seizures – from LTM

TLE - Effect of Time

Time Main Effect

$F(5,70)=3.59; p<.0060$
Intracranial EEG findings Durazzo et al, 2008

- Occipital 16:00 and 19:00
- Parietal 4:00 and 7:00
- Frontal lobe 4:00 and 7:00
- Mesial temporal lobe - bimodally, with the primary peak in the late afternoon between 16:00 and 19:00 and secondary peak in the morning between 7:00 and 10:00
- Neocortical temporal seizures peaked slightly before the primary peak observed in the mesial temporal lobe – n/s
Other recent reports

Hofstra et al, 2009 – intracranial

• Temporal lobe: 1100 - 1700
• Frontal: 2300 - 0500
• Parietal: 1700 - 2300
In Children
Seizure semiology

• Day:
  – Clonic
  – Atonic
  – Hypomotor
  – Myoclonic

• Night
  – Automotor
  – Hypermotor

Loddenkemper et al, Neurology 2010
Epileptogenic region

- Day (6:00-18:00)
  - Generalized
  - Occipital
- Night (18:00-6:00)
  - Temporal – wake
  - Frontal - sleep
Limitations of hospital recordings

• Many activities occur at regular intervals (vital signs, scheduled exams, etc.)
• Light levels are generally higher
• Many laboratories use night light to ease viewing of night time seizures
• Weaning of medications may affect timing of seizures
Ambulatory EEG - methods

• 831 records of consecutive patients’ EEGs
• Ambulatory EEG monitoring for 24-72 hours (Digitrace™ – 16 channels).
• Symptom detection:
  – log of symptoms
  – event button
• Additional EEG detection: automatic seizure and spike detection was performed on each record using Persyst detection software
Ambulatory EEG - Results

• 129 electrographic seizures
  – from 44 unique individuals
  – frontal - (31),
  – temporal (71),
  – centrally (5),
  – posterior/parietotemporal (11),
  – bilaterally or primary generalized (11).
Distribution of frontal and temporal lobe seizures over time

Pavlova et al 2011
Seizures - temporal lobe

![Bar graph showing temporal lobe seizures with age ranges 0-4, 4-8, 8-12, 12-16, 16-20, 20-24.]
Seizures – frontal lobe

Frontal lobe seizures

<table>
<thead>
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<td>16-20</td>
<td>6</td>
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<tr>
<td>20-24</td>
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Non-seizure complaints

• From push buttons only
• 1956
  – 74 - motor
  – 22 – pain
  – 80 – headaches
  – 41 – sleep related
  – 165 – concrete sensory (tingling, numbness) + 9 -vague sensory
  – 15 - cardiac (palpitations, heart fluttering)
  – 18 - sudden unexplained emotions
  – 18 – autonomic (gastric disturbance) + bulbar (choking)
  – 18 – cognitive (brief amnesia, confusion)
  – 21 – “explosions”
  – All other – vague or non-characterizable
Non-seizure Complaints

Graph showing trends of different types of non-seizure complaints over different time periods:
- Sensory
- Motor
- Dizziness
- Sleep related
- Emotions

Time periods include:
- 3 am to 7 am
- 7 am to 11 am
- 11 am to 3 pm
- 3 pm to 7 pm
- 7 pm to 11 pm
- 11 pm to 3 am

The graph illustrates fluctuations in these complaints across these time frames.
Retrospective seizure studies: summary of findings

• There are times when individual seizures occur preferentially
• These times vary by epileptogenic region – frontal in the early morning, temporal in the late afternoon
• These times are similar in the hospital as in outpatient conditions
Can endogenous circadian factors affect seizure threshold?
Challenges – how can we study circadian function in epilepsy?

• Recruitment

• Need to avoid sleep deprivation
  – Constant routine cannot be performed safely and/or yield reliable information
  – Traditional forced desynchrony may also lead to insufficient sleep

• Are circadian markers reliable?
  – LH secretion may be altered in patients with epilepsy –pulsatile with higher amplitude interictally (Quigg et al 2006)
  – Melatonin is metabolized by p450 and could potentially be affected by liver inducers

• Cost – the study cannot be performed in typical hospital conditions, as light levels cannot be controlled
Laboratory protocol
Is there a circadian variation of epileptiform discharges in generalized epilepsy?

• Pilot data: five patients with IGE
• Otherwise healthy, including no sleep disorders
• Controlled generalized seizures, no recent medication changes, stable sleep verified by 2 week actigraphy
• Four-day laboratory protocol
Results: normal melatonin profile
Results: sleep distribution
Results: circadian variation of interictal discharges
End