SLEEP, CLOCKS, AND BRAIN DISORDERS

POWERPOINT PRESENTATIONS

January 24, 2015
1:00 p.m. – 4:00 p.m.
Pointe Hilton Tapatio Cliffs Resort
Highland 2
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1. Enter your AAN ID. This can be found in the upper right-hand corner of your badge.
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- Attendees must be registered and badged to attend the individual programs.
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- CME Credits/Certificates of Attendance will be sent to attendees four to six weeks following the Regional Conference.

Program Director
Aleksandar Videnovic, MD, MSc
Boston, MA

Program Schedule and Faculty
1:00 p.m. – 1:15 p.m. Introduction
Aleksandar Videnovic, MD, MSc
Boston, MA

1:15 p.m. – 1:50 p.m. Circadian Misalignment and Sleep Disruption in Dementia
Yo-El Ju, MD
St. Louis, MO

1:50 p.m. – 2:25 p.m. Circadian and Sleep Dysregulation in Movement Disorders
Aleksandar Videnovic, MD, MSc
Boston, MA

2:25 p.m. – 2:35 p.m. Break

2:35 p.m. – 3:10 p.m. Restless Legs Syndrome as a Circadian Disorder
William G. Ondo, MD
Houston, TX

3:10 p.m. – 3:45 p.m. Circadian Rhythms and Sleep in Epilepsy
Mark S. Quigg, MD
Charlottesville, VA

3:45 p.m. – 4:00 p.m. Panel Discussion
Faculty

Program Description:
The regulation of sleep and wake states is a major function of the nervous system and has a profound influence on its activity in health and in disease. The propensity for sleep and wake are regulated by a complex interaction of the sleep homeostatic and circadian clock systems. Sleep and circadian timing are essential in modulating neural function. Recent landmark advances in our understanding of the neurocircuitry and molecular mechanisms underlying the generation of sleep and circadian rhythms have led to improved understanding of their role in the expression and treatment of neurological disorders. This program will focus on the bi-directional relationship between circadian and sleep dysregulation and neurological disorders. Presentations will feature recent exciting findings of the role of sleep and circadian timing in neurodegenerative disorders (Alzheimer’s Disease, Parkinson’s Disease, Huntington’s Disease), Restless Legs Syndrome, and epilepsy. Clinical science
for future use and research ideas will be presented, and the participants will engage actively in testing their knowledge of NOACs use.

**Learning Objectives:**
At the completion of this course, participants will be able to:
1. Understand the role of sleep and circadian rhythmicity in Alzheimer's disease
2. Discuss how circadian dysregulation and impaired sleep-wake cycle impact Parkinson's and Huntington’s disease
3. Identify circadian rhythms disturbances in Restless Legs Syndrome
4. Understand the role of sleep and circadian rhythmicity in epilepsy
5. Discuss strategies to improve circadian function in neurological disorders

**Recommended Audience:**
Academic and Practicing Neurologists; Clinical Researchers; Basic Science Researchers with an Interest in the Field

**Core Competencies:**
Patient Care; Medical Knowledge; Practice-based Learning and Improvement

**Accreditation**
The American Academy of Neurology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

**AMA PRA Credit**
The AAN designates these educational activities for a maximum number of hours in category 1 credit toward the AMA Physician's Recognition Award. The number of credits assigned to each individual program is outlined in the program's description. Each physician should only claim those hours of credit that he/she actually spent in the activity.

**Certificates for Non-Physicians**
Non-physician participating in the programs will receive a certificate of attendance indicating attendance at an activity designated for AMA PRA category 1 credit.

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**Faculty Commercial Relationship Disclosures**
- Dr. Videnovic has nothing to disclose.
- Dr. Ju has received research support from Philips-Respironics.
- Dr. Ondo has received personal compensation for activities with Teva, Ipsen, UCB, Merz, and Lundbeck as a speaker and consultant.
- Dr. Quigg has nothing to disclose.
Unlabeled Use of Product Disclosure
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Faculty Unlabeled Use of Product Disclosures
- Dr. Videnovic will not include any information on unlabeled use of products or investigational uses during the presentation.
- Dr. Ju will not include any information on unlabeled use of products or investigational uses during the presentation.
- Dr. Ondo will discuss treatments for ET (except deep brain stimulation), PSP, MSA, and CBD which are off label.
- Dr. Quigg will not include any information on unlabeled use of products or investigational uses during the presentation.
Clocks, Sleep, and Brain Disorders

Introduction

Aleks Videnovic, MD, MSc
Massachusetts General Hospital
Harvard Medical School
Boston, USA

The “two-process” model of sleep regulation
Mimosa plant

Day

Night

1729
Jean Jacques d’Ortous De Mairon
Biological Rhythms

- Periodic changes of biologic phenomena
- **Circadian rhythm** - a biological rhythm that exhibits a period of ~24 hours (circa = approximately; dies = day)
- Circadian rhythms can be described by period, phase, and amplitude.
- Genetically determined
- Entrained by **zeitgebers**
- **Chronobiology** is a field of science that examines periodic (cyclic) phenomena in living organisms and their adaptation to solar and lunar related rhythms.¹

¹ DeCoursey et al. 2003
Circadian system

Videnovic et al. 2014
Rhythmic expression of clock genes has been found in many tissues (10% of all genes) entrained by the SCN. However, the phase of the rhythm in a peripheral oscillator may differ from that of the SCN and other oscillators.

Genetics of Circadian System

SCN synchronizes peripheral tissue clocks.

Rhythmic expression of clock genes has been found in many tissues (10% of all genes).

Entrained by the SCN.

However, the phase of the rhythm in a peripheral oscillator may differ from that of the SCN and other oscillators.
Genetic components of mammalian circadian system

Videnovic et al. 2014

Importance of the circadian system

1. Observed in nearly all species
2. Regulates sleep, physiology, and behavior
3. Synchronizes organ systems at an optimal phase relationship
4. Entrains the organism to the environmental light/dark cycle
5. May contribute to daily changes in disease severity
Circadian Misalignment and Sleep Disruption in Dementia

Clocks, Sleep, and Brain Disorders
AAN Breakthroughs in Neurology
24 January 2015
Yo-El Ju, MD

Overview

• Alzheimer Disease review
• Effect of AD pathology on sleep and circadian rhythm
• Effect of sleep on risk of dementia and AD pathology
• Potential therapeutic approaches
**Dementia**: Decline in memory and other cognitive abilities sufficient to impair social and occupational functioning

Alzheimer Disease (AD) contributes to ~70-75% of cases of dementia

The looming crisis of Alzheimer Disease

*From the Alzheimer’s Association*
Risk factors for AD

- Age
- ApoE allele
- Cardiovascular disease
- Sleep?

Clinical Features of AD

- Gradual onset and progression
- Memory deficits (recent memory)
- Other cognitive dysfunction
  - executive dysfunction: problem solving, attention
  - language, praxis, visual-spatial
- Behavioral dysfunction
  - personality change, apathy
  - depression
  - delusions, hallucinations
  - sleep disruption
Probable time course of biomarkers of AD-related pathological changes in relation to clinical manifestations

<table>
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<tr>
<th>Biomarkers</th>
<th>Neuronal integrity</th>
<th>Amyloid plaques</th>
<th>Neurofibrillary tangles</th>
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- CSF TAU and pTau
- Brain atrophy (CT/MRI)
- Regional hypometabolism (FDG-PET)
- Altered brain activation (fMRI)
- Microgliosis (e.g., PK11195 PET)
- Inflammation / Oxidative Stress
- Brain amyloid (e.g., PiB PET)
- Genetic predisposition (e.g., APOE alleles, etc.)

Non-AD: Preclinical AD
Non-demented (CDR 0) Very mild AD (MCI/CDR 0.5) Mild AD (CDR 1) Mod AD (CDR 2) Sev AD (CDR 3)
Overview

• Alzheimer Disease review
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Sleep problems in AD

• Sleep problems in AD are early, common, and disruptive
• In mild to moderate AD (community-dwelling), 25-40% have sleep/wake behaviors that are bothersome to caregivers
• Daytime sleepiness causes functional impairment
• Increased daytime napping
• Sundowning
• Nocturnal wandering -> a frequent reason for institutionalization

Sleep changes with aging

- Core temperature measurement shows smaller amplitude and earlier nadir
- Aging is associated with reductions in total sleep time, sleep efficiency, and slow wave sleep.
- AD is associated with additional sleep disturbances, and a circadian phase delay


- 598 days actigraphy recording of institutionalized man with AD
- Increased activity at night, decreased activity during day
- Increased day-to-day variability
- Meds noted on left panel. Infection during section C

Obstructive sleep apnea

OSA is due to repeated collapse of the upper airway during sleep, requiring an arousal to take a breath.

Obstructive sleep apnea in AD

- OSA increases with age and is very common (>40%) in AD
- In cross-sectional studies presence of OSA is associated with cognitive impairment
- Severity of OSA correlates with severity of AD
- ApoEε4 allele increases risk of OSA and AD
- Treatment of OSA slows cognitive decline in AD

Role of sleep in cognitive functions

- Sleep stabilizes and enhances memory processes
  - NREM and REM have different roles
- Poor sleep leads to poor performance
- Abnormal sleep likely worsens cognitive performance in someone with a given level of AD pathology

AD Pathology leads to sleep and circadian disturbances

- Amyloid plaques and tangles are found in brain regions critical for sleep-wake functions and circadian control
- Polysomnography in AD shows decreased REM sleep, decreased slow wave non-REM sleep, and increased sleep fragmentation
- EEG during wake is slower in AD
Markedly increased wakefulness with increasing Aβ pathology in PSAPP mice

Sleep decreases and wakefullness increases with plaque deposition and age while ISF Aβ fluctuation is attenuated

Aβ vaccination decreases plaques in PS/APP mice


Aβ vaccination prevents sleep/wake abnormalities in PS/APP mice

Amyloid deposition attenuates diurnal Aβ variation in humans


Sleep quality is reduced in preclinical AD

- 145 cognitively normal adults aged 65.6±8.2 yrs
- 32 had biomarker evidence of amyloid plaques, ie preclinical AD
- Actigraphy x 2 weeks
- Total sleep time was not different between groups
- Sleep efficiency (sleep time / time in bed) was significantly reduced, 80% vs 84%, in those with preclinical AD
- Worse sleepers had 5.6 odds ratio of having preclinical AD

Sleep disturbance is associated with amyloid deposition.

- Self-reported sleep of 70 community-dwelling adults
- PiB-PET to assess amyloid deposition
- Short sleep duration associated with greater amyloid burden
- Self-reported lower sleep quality also associated with greater amyloid burden in the precuneus

Summary

- Sleep-wake and circadian abnormalities are common and disruptive in AD
- Sleep disturbance may further impair cognitive ability in AD
- High prevalence of OSA in AD
- AD pathology leads to sleep disturbance in mouse models, and reversing pathology improves sleep
- Sleep quality is reduced in preclinical AD in humans
Overview

- Alzheimer Disease review
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- Potential therapeutic approaches

Abnormal sleep is associated with dementia risk in humans

- Cross-sectional studies
  - Sleep duration: Guanzhou study N=28670 (50-85yo) sleep 3-4 or >10 hours had worse delayed word recall (OR 1.29; 1.52)
  - Sleep quality: Study of Osteoporotic Fractures (SOF) 2932 elderly (mean 83.5y) women: sleep efficiency <70% had poor MMSE <26 (MOR 1.6) and Trails B (MOR 1.96)
  - OSA: SOF - Severe OSA (AHI > 30) AOR of 3.4 for worse MMSE/trails B performance

Abnormal sleep is associated with dementia risk in humans

- Prospective studies
  - Sleep quality: SOF 15% developed preclinical cognitive decline – MOR 1.7 for sleep efficiency <70%, MOR 1.57 sleep latency >1h, MOR 1.43 for WASO >90min
  - OSA: SOF N=298 starting with no MCI or dementia
    - All women, mean age 82.3 ±3.2, followup 4.7y
    - 20.1% developed MCI, 15.8% dementia
    - OSA (AHI >15) increased risk of developing MCI/dementia (AOR 1.85)
    - Oxygen desaturation and not indices of arousals were associated with MCI/dementia risk


Abnormal sleep is associated with dementia risk in humans

- 737 community dwelling cognitively normal adults.
- Actigraphy data used to calculate “sleep fragmentation index.”
- Over followup of mean 3.3 years, 13% developed dementia.
- Those in the 90th percentile for sleep fragmentation had 1.5 risk of developing dementia as those in 10th percentile.

Due to the long preclinical period, “prospective” studies in humans so far are actually cross-sectional.
Aβ fluctuates during sleep/wake cycles

Kang et al. Science 2009 326:1005-1008

Regional ISF Aβ levels are proportional to a marker of neuronal activity

CNS infusion of orexin increases ISF A\textsuperscript{β} and minutes awake

Kang et al. Science 2009 326:1005-1008

CNS infusion of the dual orexin receptor antagonist, Almorexant, decreases ISF and wake time

Kang et al. Science 2009 326:1005-1008
Sleep deprivation markedly increases amyloid plaques in PS1/APPswe Tg mice

Kang et al. Science 2009 326:1005-1008

Diurnal variation of Aβ in humans

Sleep deprivation in humans leads to increased Aβ levels


Adapted from Buckner et al., J Neurosci, 2005.

Default network (cognitively normal adults) → Amyloid deposition (Alzheimer’s disease)

Adapted from Buckner et al., J Neurosci, 2005
Glymphatic system clears metabolites, including Aβ, during sleep


[Diagram]

Sleep disturbance

Increased neuronal activity

Decreased glymphatic clearance

Increased Aβ release

Increased Aβ levels

Cardiovascular stress

APOEε4 allele

OSA

Age

Decreased cognitive and physical activity

Injury to sleep/circadian brain regions

Amyloid deposition

Cognitive dysfunction/ Symptomatic AD

[Graph A: Graph B:}
Overview

• Alzheimer Disease review
• Effect of AD pathology on sleep and circadian rhythm
• Effect of sleep on risk of dementia and AD pathology
• Potential therapeutic approaches

Current therapeutic options

• Identify and treat primary sleep disorders
  – Treatment of OSA, if tolerated, does improve AD outcome
• Behavioral: “sleep hygiene”, light exposure, exercise/activity, caffeine, etc
• Medications tested for sleep in AD
  – Melatonin and ramelteon showed no improvement
  – Trazodone 50mg improved total sleep time and sleep efficiency, but not daytime function measures
  – No other more typical hypnotics (NBBRA's) have been tested in AD
Future therapies

• Specifically test treatments for sleep-wake and circadian abnormalities in AD
  – Daytime therapies may be effective, not just nighttime symptomatic medications
• Target the interconnected mechanisms between sleep and AD
• Goal is not just symptomatic relief, but to slow progression of AD

Future therapies

• Therapies to prevent or slow AD have been very disappointing.
• Treatments are more likely to be effective during the preclinical phase of AD
• Sleep features may be used as a marker to identify those with preclinical AD who are most likely to benefit from treatment, or to follow brain pathology noninvasively.
• If a sleep-related therapy can slow progression of AD pathology, it may be possible to delay progression into the symptomatic phase of AD, thereby “preventing” AD.
Summary

• AD is a common cause of dementia, and AD pathology at the earliest (preclinical) stages is associated with sleep abnormalities
• Disrupted sleep appears to increase the risk of AD
• Recent research shows Aβ is acutely affected by sleep and may mediate the reciprocal relationship between sleep and AD
• Several new exciting avenues for therapies directed at sleep and AD.
Circadian and Sleep Dysregulation in Movement Disorders

Aleks Videnovic, MD, MSc

Massachusetts General Hospital
Harvard Medical School
Boston, USA

Conflict of Interest Disclosures

- Dr. Videnovic does not have any potential conflicts of interest to disclose.
Study of sleep dysfunction in PD
- challenges -

• Under-diagnosed and under-reported problem
• Heterogeneous population
• Etiology of sleep dysfunction
  – Co-existent, independent disorders of sleep and alertness
  – Effects of the primary neurodegenerative process of PD on centers regulating sleep and alertness
  – Influence of PD symptoms / signs / medications on sleep and alertness
• How to measure sleep dysfunction?

Parkinson’s disease

• 1,000,000 affected in US
  • Incidence 15-20 / per 100,000
  • Prevalence 360 / 1,000,000
• Prevalence increases with age (per 100,000)
  • 40- 49 yo: 23
  • 70- 79 yo: 525
  • 80- 89 yo: 1145
• Geographic distribution varies
Parkinson’s disease

• Symptoms
  – Motor: tremor, slowness, stiffness, gait disturbance
  – Non-motor: sleep/wake dysfunction, depression, autonomic dysfunction, psychosis

• Many biological rhythms and symptoms of PD demonstrate profound diurnal fluctuations

• Emerging evidence suggest that dopamine (DA) plays an important role in the regulation of circadian system

Is Parkinson’s disease affected by chronobiology?

Pathology

Braak et al. 2003
Is Parkinson's disease affected by chronobiology?

- Approaches to answer the question
  - Observations related to symptoms and signs of PD
  - Study of biologic markers of circadian rhythmicity in PD
  - Effects of modulators of circadian system on PD
Sleep - Wake Cycle in PD

• Nocturnal sleep disturbances in PD
  - 60% of patients versus 30% of healthy controls
  - Insomnia, mainly sleep maintenance, most common disturbance
  - RBD – harbinger of parkinsonism

• Excessive daytime somnolence (EDS)
  - 16% of patients versus 1% of healthy controls
  - EDS has been associated with three-fold increase in the risk of developing PD

• Sleep Benefit – improvement in motor symptoms the morning after drug intake at night
  - Mechanisms ???

Disturbed sleep - wake cycle in PD
- Pathophysiology -

• Symptoms of PD
• Complex medication regimens
• Co-existent sleep disorders
• Age related changes in sleep architecture
• Primary neurodegeneration of PD
  – Central sleep regulation centers
    – Locus coeruleus
    – Raphe nucleus
    – PPT nucleus
    – Hypothalamus (hypocretin)
Disturbed sleep - wake cycle in PD
- Pathophysiology -

- Symptoms of PD
- Complex medication regimens
- Co-existent sleep disorders
- Age related changes in sleep architecture
- Primary neurodegeneration of PD
  - Central sleep regulation centers
    - Locus coeruleus
    - Raphe nucleus
    - PPT nucleus
    - Hypothalamus (hypocretin)
    - Circadian system (SCN and its pathways) ??
Diurnal motor activity in PD

Van Hilten et al. 1991

Circadian dysfunction in a mouse model of Parkinson’s disease

Takashi Kudo, Dawn H. Loh, Danny Truong, Yingfei Wu, Christopher S. Colwell

Department of Psychiatry & Biobehavioral Sciences, University of California-Los Angeles, Los Angeles, CA 90024, USA
Is Parkinson’s disease affected by chronobiology?

- Approaches to answer the question
  - Observations related to symptoms and signs of PD
  - Study of biologic markers of circadian rhythmicity in PD
  - Effects of modulators of circadian system on PD

Biologic markers of circadian rhythmicity

- Melatonin
- Cortisol
- Temperature
- Circadian clock genes

Experimental design
- Forced desynchrony
- Free run
- Constant routine
Circadian rhythm - melatonin

Breen et al. 2014

Circadian rhythm - melatonin

Videnovic et al. 2013
Circadian secretion pattern of cortisol in PD

Clock genes in PD

- Tyrosine hydroxylase is under the control of molecular clock \(^1\)
- Activation of D\(_2\) DA receptor:
  - modulates the circadian effects of light on locomotor activity in mice \(^2\)
  - regulates expression of clock genes in retina and striatum \(^3\)

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\(^{1}\) Doi et al. 2006
\(^{2}\) Besharse et al. 2004; Yujnovsky et al. 2006
\(^{3}\) Imbesi et al. 2009; Sahar et al. 2010
Clock genes in PD

- Depletion of striatal DA by 6-hydroxydopamine or blockade of D_{2} DA receptors by raclopride abolishes the circadian rhythm of Per2 gene.

- Activation of D_{2} DA receptors restores and entrains the Per2 rhythm in the DA-depleted striatum of mice.

Hood et al. 2010
Clock Genes in PD

Per1

Bmal1
Clock Genes in PD

Breen et al. 2014
Is Parkinson’s disease affected by chronobiology?

- Approaches to answer the question
  - Observations related to symptoms and signs of PD
  - Study of biologic markers of circadian rhythmicity in PD
  - Effects of modulators of circadian system on PD

Light exposure and PD
Light exposure and PD

- Connections between the visual system and DA systems can increase activity on exposure to bright light. ¹,²,³
- Improvements in motor performance observed in experimental animals by housing them in a constant ambient light. ⁴
- Administration of bright light to patients with PD improves bradykinesia, rigidity and depression scores. ⁵,⁶,⁷
- Most effective frequencies of light are most likely in the blue/green spectrum (500 nm), the frequencies affected in the visual deficits in the PD population. ⁸

Huntigton’s disease

- 14 -16 / 100,000
- Abnormal expansion of CAG repeat
- Motor, cognitive, neuropsychiatric symptoms
- Progressive weight loss
- Impaired sleep-wake cycles
  - Increased sleep latency
  - Low sleep efficiency
  - Excessive sleepiness
  - Abnormal sleep architecture
- How about circadian rhythmicity?
Melatonin rhythm in HD

Azizi et al. 2009

SCN in HD

Van Wamelen et al. 2013

Kudo et al. 2011
Abnormal circadian activity in HD patients

Morton et al., 2005

Disruption of circadian activity pattern in R6/2 mice

Morton et al., 2005
Impaired circadian gene expression in SCN of R6/2 mouse

Pharmacological imposition of sleep reverses dysregulation of circadian gene expression in HD
Temporally scheduled feeding restores disruption of peripheral circadian timekeeping in HD

Maywood et al., 2010

Conclusions

• Clinical and physiologic studies suggest significant modification of circadian system in PD and HD.

• This disruption is accompanied by marked disruption of expression of the circadian clock genes in the CSN and peripheral tissues.

• Further studies are needed to investigate behavioral, physiologic and genetic aspects of circadian function simultaneously with motor, psychiatric, cognitive, autonomic and sleep functions in the PD population.

• This systematic approach may lead to development of novel circadian-based treatments for PD.
The second iceberg is emerging.
Restless Legs Syndrome

William Ondo MD
Prof. Neurology, University of Texas Health Science Center at Houston, Director - WED/RLS Quality Care Center, Houston

Grant Support: Ipsen, UCB Pharma, PSG, HSG
Speaking/Consulting fees: Ipsen, TEVA, UCB Pharma, Merz, Abbvie

Clinical Definition

- Urge to move the legs with or without paresthesias
- Symptoms worse during inactivity
- Symptoms improve with activity
- Worsening of symptoms in evening and night
Supportive Criteria

- Sleep disturbances
- Normal neurologic examination
- Chronic progressive course
- Periodic limb movements of sleep (PLMS)
- Family history
- Dopamine response

Clinical Description (Paresthesias)

- Need to move
- Crawling
- Tingling
- Cramping
- Creeping
- Pulling
- Painful
- Electric
- Tension
- Discomfort
- Itching
- Heebie Jeebies
- Wriggling maggots
- Fidgets
- Elvis legs

Ondo W. 1996
Clinical Descriptions

• Usually between knees and feet
• Deep sensation (90%)
• Bilateral, unilateral or alternating
• Arms may be involved (22%-57%)
• Periodic Limb Movements of Sleep (PLMS)

PLMS
PLMS/RLS and Cardiovascular Disease

- **Sleep Heart Health Study**
  - CVD were 2.07 (95% CI: 1.43 to 3.00)
  - CAD were 2.05 (95% CI: 1.38 to 3.04)

- **PLMS**: Assoc. with small vessel disease (NP)

- **Mechanism:**
  - PLMS: SBP>20, DBP>10, Increased RR variability
  - Improved with dopaminergics (NP)


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PLM / Dyskinesia While Awake / Stereotype
Severe RLS

Differential Diagnosis

- Akathisia
- Painful legs and moving toes
- Nocturnal leg cramps
- Growing pains
- Attention deficit hyperactivity disorder
- Vesper’s curse
- Orthostatic hypotension
- Orthostatic tremor
- PLMS without RLS
- Psychogenic
RLS in Children

• No definitive epidemiology (1-2%)
• Many children do not meet criteria for adult RLS
• May present with:
  – “growing pains”
    • Associated with low ferritin and PLMS
  – Attention deficit hyperactivity disorder

Picchietti D, 2013

RLS and ADHD

• ADHD Children have:
  – Greater PLMS
    • 26% have >5/hour
  – Worse sleep in general
  – 32% have a parent with RLS
  – Lower ferritin

## Epidemiology of RLS

- **REST** = 9.6% (U.S. Europe)
- **Hogl** = 10.2% (Austria)
- **Berger** = 10.6% (Germany)
- **Rothdach** = 9.8% (Germany)
- **Phillips** = 10.0% (Kentucky)
- **Stepansky** = 7.9% (Austria)
- **Lavigne*** = 10-15% (Canada)
- **Ulfberg** = 5.8% m 11.4% w (Sweden)
- **Tan** = <1% (Singapore)
- **Kageyama** = 1.5% (Japan)

### Epidemiology (REST Study)

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RLS Pathophysiology

- Genetic Evaluation
- Pharmacologic Response
- Animal Models
- Imaging
- Functional Studies
- Pathology
- Circadian Physiology
### Genetics of RLS, Genome-Wide Association Study

![Genetics of RLS, Genome-Wide Association Study](image)

**Winkelman et al., Plos Genet 2011**

### Genome Wide Associations

<table>
<thead>
<tr>
<th>Chrom</th>
<th>Gene</th>
<th>O.R.</th>
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<th>Description</th>
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<td>Zinc Finger</td>
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<td>Near MEIS1</td>
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<td>Non-histone chromatin</td>
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</table>

Animal Models of RLS?

A11 Spinal Projections

- A11
- Intermedial-lateral tract (autonomic)
- D1/D2
- D3
- Dorsal Root Ganglion
- D1
- Motor Neuron
A11 Lesioning

Sham Lesion

6-OH-Dopa Lesion

A11 6-OH Lesioned Mice on Left
Human Neurologic Studies

- Normal gross MRI
- No Bereitschaftspotential (BP) preceding DWA
- No cortical back-averaged potentials in PLMS
- Near normal electrical blink reflex
- Normal BAER and SSEP
- Normal H reflex, H/M ratio

PET / SPECT Studies

- Dopamine transporter protein
  - 3 SPECT normal studies, one PET abnormal
- $^{18}$F-dopa PET
  - 2/3 Studies: mild striatal reduction
- $^{11}$C-raclopride
  - mild striatal reduction
- $^{123}$I-iodobenzamide SPECT
  - 1/2 studies: mild reduced striatal D$_2$ binding
MRI (mixed data)

- Mildly increased pulvinar grey volumes ¹
- Decreased bihemispheric primary somatosensory cortex grey matter ²
- No volumetric changes ³
- No volumetric changes ⁴
- Increased fractional anisotropy in diffuse white matter ⁵


Figure 2. R2* images in (A) a 70 year old RLS patient and (B) a 71 year old control subject. Much lower R2* relaxation rates are apparent in the RLS case in both red nucleus and substantia nigra. (Allen RP, Earley CJ and Barker P Johns Hopkins Univ.)
Ultrasound showing decreased echogenicity in the midbrain area of the nigra for RLS compared to control

Fig 2. Typical examples of transcranial ultrasound appearance (axial scanning plane) in three patients. (A) Patient with Parkinson's disease (PD). (B) Normal control subject (C0). (C) Patient with restless leg syndrome (RLS). Midbrain and areas of hyperechogenicity circled in (A) and (B) on the side of isoaution.


RLS Human Pathology
Tyrosine Hydroxylase Staining in Normal vs RLS Substantia Nigra

H-ferritin
L-ferritin
Transferrin and Transferrin Receptor Expression in Neuromelanin cells isolated from Substantia Nigra
Orexin increased in RLS


Iron in Human Brain (Perl’s Rxn)

Iron and Dopamine

- Co-factor for tyrosine-hydroxylase
  - Rate limiting step for dopamine synthesis
- Component of the D2 receptor
  - Down-regulates D2 receptors
  - Changes behavior
- Thy-1 reduced
  - Involved in dopamine release

Thy1 expression in total brain homogenates of mildly iron deficient rats and substantia nigra of human brains (control and RLS)
Circadian RLS Clinical

• There is a true circadian pattern
• Sleep deprived sensory immobilization data:
  – Worse 11 PM to 4 AM
  – Best: 8 AM -2 PM
• RLS worse after sleep deprivation

Hening W 1999, Trenkwalder C 1999

Circadian Physiology in RLS

• No difference in core body temperature vs. controls
• Relatively enhanced nocturnal cortisol excretion in RLS compared to controls
• Transcranial Magnetic Stimulation
  – During day, similar to controls
  – At night reduced cortical silent periods, motor thresholds tended to decrease

Circadian Abnormalities in RLS (dopamine and iron)

• Most data suggests CSF circadian properties: most suggest peak in late AM /reduction at night
  – RLS subjects greater change in 3-OMD between day and night
  – Nocturnal L-dopa administration inhibits prolactin release at night in RLS more than controls
• Serum iron nadirs early night (all people)
  – Brain Iron decreases in light (sleep) phase- mice


Circadian RLS (Conclusions)

• There seems to be an exaggerated dopaminergic circadian cycle
  – Relatively lower at night
  – Relatively higher in day
• Iron may also fluctuate
• There may also be homeostatic drive influence in addition to circadian drive
Secondary Causes of RLS

- Iron deficiency
- Renal failure
- Neuropathy
- Pregnancy
- Multiple sclerosis
- Essential Tremor
- Parkinson’s Disease
- SCA – 3 (Machado-Joseph)

Ferritin Model with other FE species
Measuring Serum Iron is Difficult

• Ferritin:
  – Acute phase reactant can be elevated for 6 weeks
  – Increased with age (should be greater than age)
  – Increased with decreased GFR (renal function)

• Iron:
  – 50% higher in AM compared to night
  – Increased after meal

• Iron binding percentage:
  – Formula with iron, TIBC, transferrin

Serum Ferritin and RLS

• Late Onset of RLS (Non-familial)
  • Lower serum ferritin
  • Severity correlated with serum ferritin levels

• Early onset of RLS (Familial)
  • Normal serum ferritin
  • Severity not correlated with ferritin levels
Medications

- Anti-histamines
- Dopamine blockers
- Anti-depressants

Treatment of Restless Legs Syndrome
RLS Treatments

- Dopamine Agonists
- L-dopa
- Opioids
- Benzodiazepines
- Gabapentin (Enacarbil)
- Valproate
- Tramadol
- Carbamazepine
- Clonidine
- amantadine

- Iron (oral, IV)
- Mg++
- Sclerotherapy
- TENS unit
- Thermal therapy
- Cognitive Activation

IRLS Placebo Response

<table>
<thead>
<tr>
<th>Country</th>
<th>N</th>
<th>Mean (SD)</th>
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<tbody>
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<td>Finland</td>
<td>65</td>
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<td>Ireland</td>
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<td>Austria</td>
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<td>France</td>
<td>15</td>
<td>5.07 (8.02)</td>
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<tr>
<td>MEAN</td>
<td>879</td>
<td>9.51 (9.78)</td>
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</table>

Predictors: greater IRLS score (p<0.001), absence of previous dopaminergics (p<0.001), female sex (p=0.05), randomized drug: placebo ratio of >1:1 (p<0.001), and trials in America (p<0.001)

Ondo W 2012
Levodopa/Carbidopa (Sinemet)

- 12 controlled trials demonstrate efficacy

Dopaminergic Side Effects

- NO dyskinesia
- NO psychosis (hallucinations)
- Minimal orthostatic hypotension
- Mild impulse control disorders (gambling)
- Nausea, sedation, nasal congestion
- Augmentation
Augmentation

- Worsening of symptoms after initial therapeutic benefit not accounted for by other factors
- Earlier onset of symptoms (<4 hours) OR,
- Earlier onset of symptoms (>2 hours) AND one
  - Shorter latency to symptoms when at rest
  - Extension to other body parts
  - Greater intensity
  - Less relief from treatment

Risks for Augmentation in Dopamine Agonists

- Family history of RLS
- Lack of Neuropathy
- Dopamine dose
- Low ferritin (iron)
- Shorter acting dopaminergics
Dopamine Agonists

- Ropinirole (Requip / Requip XR)
- Pramipexole (Mirapex / Mirapex ER)
- Rotigotine (Neupro patch)
- Pergolide (Permax)
- Bromocriptine (Parlodel)
- Cabergoline (Dostinex)
- Apomorphine (Apokyn injections)
- Lisuride / Sumanirole

Rotigotine / Pramipexole / Ropinirole (Comparisons)

- Overall results are similar
  - International RLS Rating Scale
  - Clinical Global Impressions
- All studies have large placebo response
- Rotigotine had a modestly higher percentage of complete responders
- Mirapex ER and Requip XR not tested in RLS
PLMS After Pramipexole

Dopamine Agonist Strategy

- Time dose according to symptoms
  - usually 1-3 doses
- Titrate to lowest dose that stops symptoms
- Avoid continuous dose augmentations after effective treatment initially achieved
- Consider rotating different dopamine agonists
Opioid Treatments for RLS

Opioids: A Long History

- Used by Willis in his first description of RLS
  - “…‘leapings and contractions of the tendons, and so great a restlessness and topplings of their members ensue that the diseased are no more able to sleep than if they were in a place of the greatest torture’” 1685
  - Tincture of opium

Willis T. Two discourses concerning the soul of brutes 1683
Opioid Overview

- May treat sensory more than motor symptoms
- Mu opioids probably more effective
- Extended oxycodone-naloxone best studied
- Usual adverse events: Constipation
- Dose often very stable over many years
- Addiction and dependency relatively uncommon

Trenkwalder C, Lancet Neurol 2013

Methadone: Continued Long Term Benefit and Lack of Augmentation

Mean dose 10 mg, minimal increase over time

Silver N. Sleep Med 2011
Alpha-2delta Subunit Voltage Gated Calcium Channel

Gabapentin, Gabapentin enacarbil, Pregabalin

Gabapentin RLS Patient Studies

<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Trial Design</th>
<th>N</th>
<th>Baseline RLS Severity</th>
<th>Results for GBP-Treated Patients</th>
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<tbody>
<tr>
<td>Micozkadioglu (2004)</td>
<td>RCT, OL</td>
<td>14*</td>
<td>Moderate</td>
<td>Decrease in RLS severity in all patients†</td>
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<td>Improvements in sleep quality,† sleep latency,‡ and sleep duration†</td>
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<td>Happe (2003)2</td>
<td>RCT, OL</td>
<td>16</td>
<td>Moderate to severe</td>
<td>Decrease in RLS severity in all patients†</td>
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<td>Reduction in PLMS§</td>
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<tr>
<td>Garcia-Borreguero (2002)3</td>
<td>RCT, DB, CO</td>
<td>22</td>
<td>Moderate to severe</td>
<td>Decrease in RLS severity§ and stage 1 sleep§</td>
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<td>Reduction in PLMS§ and improvements in increased total sleep time,§ sleep efficiency,¶ and slow wave sleep§</td>
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<tr>
<td>Thorp (2001)4</td>
<td>RCT, DB, CO</td>
<td>13*</td>
<td>Not defined</td>
<td>12 of 13 patients had relief of RLS symptoms§</td>
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<tr>
<td>Happe (2001)5</td>
<td>OL</td>
<td>9</td>
<td>Moderate to severe</td>
<td>8 of 9 patients had relief of RLS symptoms,† increased sleep quality,‡ and decreased daytime sleepiness††</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Reduction in PLMS‡‡</td>
</tr>
<tr>
<td>Adler (1997)6</td>
<td>OL</td>
<td>8</td>
<td>Not defined</td>
<td>4 of 8 patients had relief of RLS symptoms</td>
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</table>

Abbreviations: GBP indicates gabapentin; RCT, randomized controlled trial; OL, open-label; PLMS, periodic limb movements of sleep; DB, double-blind; CO, cross-over.

Gabapentin Enacarbil (Horizant)

- Gabapentin prodrug, which is actively transported by MCT1 and SMVT
- Well absorbed throughout gastrointestinal (GI) tract
- Immediately releases gabapentin in blood
- Linear pharmacokinetics (no saturable absorption of gabapentin)
- Successfully formulated for sustained release (SR)
- 2 mg of XP13512 produces ~1 mg of gabapentin

MCT1 indicates monocarboxylate transporter type 1; SMVT, sodium-dependent multivitamin transporter.

Mean Concentrations of Serum Gabapentin After Oral Near-Equal Gabapentin Enacarbil or Gabapentin in Healthy Adults

- 2-fold increase in AUC
- 3-fold delay in $T_{\text{max}}$
- Bioavailability, 75%

2 mg of gabapentin enacarbil ~1 mg of gabapentin.

AUC indicates the area under the plasma concentration-time curve; $T_{\text{max}}$ time to maximum plasma concentration. XenoPort, Inc., Study XP022, data on file.
Pregabalin vs. Pramipexole

- 12 week PC trial; 40 week extension for augmentation
  - Pram: 0.25mg, 0.5 mg, Pregab 300 mg
- IRLS: Preg (4.5), Pram 0.5mg (3.2), 0.25 (.6)
- AE drops: Pregab (28%), Pram .25 (19%) Pram .5 (24%)
- Augmentation: (52% drop-out)
  - Pregabalin (2.1%)
  - Pramipexole 0.25 mg (5.3%)
  - Pramipexole 0.5 mg (7.7%)

Allen R NEJM 2014

Alpha-2 Deltas vs. Dopaminergics

- Similar overall improvement in IRLS and CGI
- Dopaminergics:
  - better PLMS reduction
  - “urge to move” almost always improves
- Gabapentin:
  - Sleep architecture (SWS) improves
  - Pain improves
  - Less augmentation?
Iron

- Oral iron very poorly absorbed
  - Empty stomach
  - Avoid divalent cations including calcium, MVI
  - Organic preparations
- Intravenous iron
  - Markedly increases serum iron
  - Mixed data in studies
  - Iron dextran probably superior

Iron Preparations

- Intravenous:
  - Iron dextran-low molecular weight (Infed)
  - Iron dextran-high molecular weight (Dexferrum)
  - Iron Sucrose (Venofer)
  - Ferric gluconate (Ferrlecit)
  - Ferumoxytol (Feraheme)
  - Ferric carboxymaltose (Ferinject)
- Oral
  - Iron sulfate, iron sucrose, iron fumarate, iron gluconate, iron dextran, ferroglycine sulfate
RLS Conclusions

• Very common and under diagnosed
• Ask about symptoms
• Interesting pathophysiology
• No “cure” but rewarding to treat
The Chronobiology of Epilepsy

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Professor of Neurology
Medical Director Neurophysiology Lab
Department of Neurology
University of Virginia
Charlottesville, VA, USA

Disclosures:

• Funding NIH-NINDS, NIH-NIMH
Outline

- What are the effects of circadian rhythms on epileptic seizures?
- What are the effects of epilepsy or seizures on circadian rhythms?
- Can attention to circadian timing provide benefits to patient management?
Definitions

- **Circadian**: rhythm persists in absence of time cues (endogenous)
- **Chronotype**: preference for a particular timing of activity *(early morning, neutral, evening)* tied to underlying circadian timing
- **Daily / diurnal**: rhythm attenuates once time cues are removed (exogenous)
- **State**: sleep (REM, NonREM) and wakefulness
- **Rigorous definition of circadian** requires that phenomenon be examined in a time cue-less environment *(free-running)*. In the strict sense, time-of-day phenomena is not equivalent to circadian phenomena

- Most publications about circadian phenomena of epilepsy do not distinguish between **state** and **timing** and whether patterns are independent

---

Circadian distribution of seizures in partial epilepsy

- **Time of day of occurrence of EEG-confirmed limbic seizures**
- **Epileptic rats**: 547 seizures, 20 rats, diurnal distribution
- **MTLE**: 774 seizures, 64 subjects, diurnal distribution

*Quigg M et al. Annals Neurol 1998;43:748-55*
Circadian distribution of seizures in partial epilepsy

- Both animal models of limbic epilepsy and humans with MTLE have daytime peaks of seizure occurrence in the afternoon.

- **In-phase seizure patterns**, in spite of **out-of-phase rest-activity cycles**, suggests that modulatory influence is less likely to be sleep-related and more likely to be those that maintain same phase across species (**circadian timing system effects**).

Circadian distribution of seizures in epileptic rats

- Phase-time of occurrence of EEG-confirmed limbic seizures in 11 rats.
- LD: 1378 seizures.
- DD: 1827 seizures.
- Spontaneous limbic seizures occur in a phasic pattern that persisted after removal of time cues.

*Quigg M et al. Epilepsia 2000;41:505-9*
Circadian regulation of IEDs in JME: forced desynchrony

- 3/5 patients had enough IEDs to study
- Most IEDs during NREM
- In those patients with sufficient data, circadian variation present in wake and NREM (variation of polyspikes within same state at different circadian times)
- Peak phase of polyspikes different among patients

Pavlova et al, Epi Behav 2009
Effects of circadian timing and sleep state on seizure expression

- Given that there is evidence of circadian seizure regulation, what circadian/diurnal patterns exist?
- How do circadian influences interact with sleep (NREM, REM) and wake?

State effects: NREM sleep activates spikes

- IED rate rises during NREM, falls during REM (Kellaway 1985, Stevens 1974)
- NREM sleep activates IIED (Malow 1999)
- Synchronization in NREM facilitates seizure-like discharges (Steriade 1993)
- Polyspikes during forced desynchrony most common during NREM (Pavlova 2009)

Kellaway 1985
Effects of sleep stages on seizures: NREM sleep activates seizures, REM inhibits

- NREM facilitates seizure occurrence, REM inhibits seizure occurrence
  - Herman et al, Neurology 2001
  - Sammaritino et al, Neurology 1991
  - Montplaisir et al, Sleep and Epilepsy 1982

- NREM associated with greater incidence of secondarily generalized seizures
  - Herman et al, Neurology 2001

Sleep facilitates frontal lobe seizures and promotes secondary generalization of partial seizures

Figure 2. Percentage of partial seizures arising during sleep from various seizure types across frontal lobe epilepsy (n = 115); TLE = temporal lobe epilepsy (n = 305); MTL = mesial temporal lobe epilepsy (n = 164); NLE = nonconvulsive lobar epilepsy (n = 61); OLE = occipital or parietal lobe epilepsy (n = 45). Grey bars, absence; black bars, absence. *p < 0.05; **p < 0.001; ***p < 0.001.

Figure 3. Percentage of partial seizures undergoing secondary generalization during various sleep stages. Although all NREM sleep stages appeared to promote secondary generalization, Stage 2 sleep had the most marked effect (*p < 0.001). Black bars, complex partial seizures with secondary generalization.

Herman et al, Neurology 2001
The modulatory effects of circadian rhythms on seizure precipitation: patterns of seizure timing are a complex interaction between the CTS, underlying hormonal rhythms, and sleep/wake state

Effects of circadian timing/sleep on expression of seizures

- Few studies have defined effects of CTS clearly distinct from that of sleep-wake state
- Epileptic seizures have a clear diurnal or nocturnal preference of occurrence that varies with epilepsy syndrome
  - **Mesial temporal lobe epilepsy** has a diurnal pattern of occurrence that fulfills criteria for truly circadian occurrence
  - **Extratemporal focal epilepsies**, especially of frontal lobe origin, preferentially occur during sleep
- Many **generalized epilepsies** are facilitated by transitions from sleep to wakefulness and have evidence of circadian occurrence
- Patterns in adult epilepsies do not always match with those of children
Daily distribution of seizures in partial epilepsy

- Time of day of occurrence of EEG-confirmed partial-onset seizures
- XTL: 465 seizures, 26 subjects, “random distribution”
- MTLE: 774 seizures, 64 subjects, diurnal distribution


Similar differentiation of limbic vs nonlimbic foci in other studies of adults


- In general, with focal epilepsies
  - Limbic: day/circadian mediated
  - Nonlimbic focal: night/sleep mediated
Daily distribution of partial seizures: children and adults

First study to demarcate children from adults

Children appear to have a bimodal rhythm that is more pronounced in XTLE

Since epilepsies change with developmental age, it’s reasonable to expect circadian effects to change


Generalized seizures in children

- Tonic and tonic–clonic seizures sleep > wake
- Abs, IS, atonic, myoclonic, clonic wake > sleep
- Bimodal
  - Clonic, IS: 0600–0900/1200-1500
  - Abs: 0900-1200, 1800-2400
- Single peak
  - Atonic: 1200-1800
  - Myoclonic: 0600-1200

The effects of seizures on circadian rhythms

Timex speed boat challenge: “Takes a licking but keeps on ticking”

Effects of seizures and epilepsy on CTS

- CTS abnormalities may include shifts of expected phases of peak endocrine secretion, attenuated amplitudes of circadian rhythms, disordered patterns of secretion, sleep/wake abnormalities, or underlying defects in the genetic clock.

- CTS abnormalities have not been demonstrated consistently

- Both seizures and the underlying lesion of MTLE may contribute to dysregulation of the CTS.

- Phenotype of these effects (sexual, cognitive, sleep, mood) is not known.
Effects of seizures on circadian rhythms

6 patients with TLE in an epilepsy unit

Melatonin peak lower in interictal state and increased postictally

• No effect on timing of subsequent peak (3 hour intervals)

• Cortisol levels increased postictally

• Bazil et al. 2000

Effects of epilepsy and seizures on hormonal patterning

• Hypothesis:
  • Seizures perturb appropriate secretion of hormones
  • The epileptic lesion alters normal secretion of hormones

• Methods
  • ControlA/B
  • Epileptic baseline
  • Epileptic postictal

Quigg et al, Annals Neurol 2002
Effects of seizures on peak cortisol secretion

Complex partial seizures may significantly alter time of peak cortisol secretion

Phase of peak cortisol secretion in 10 men w/MTLE

Quigg et al, Annals Neurol 2002

Effects of seizures on peak LH secretion

Complex partial seizures significantly alter time of peak LH secretion

Phase of peak LH secretion in 10 men w/MTLE

Quigg et al, Annals Neurol 2002
Seizures and phase shifts in CRT

Unlike PRC induced by light, shifts following seizures in kindled rats are variable, especially at phase after CRT peak.

Stewart et al, Epilepsy & Behavior 2003

Acute phase shifts after status epilepticus

Increased locomotor activity following pilocarpine induced status in light and dark phases. Seizures caused phase delays in activity.

Stewart et al, Epilepsy & Behavior 2003
Changes in circadian rest activity patterns in the EMU

Wrist actigraphy shows possible changes in patterns of circadianally mediated rest-activity after bursts of complex partial seizures (v)

Labelling of activity-onset by blinded review

Data: Quigg unpublished

Alterations in clock genes in epileptic mice

Work in an epileptic mouse model: mouse model of spontaneous limbic epilepsy (kcna-1 knockouts)

1. Circadian rhythm of seizures across the 24 hr cycle in an LD/light synchronized environment

2. Circadian rest activity patterns are disrupted in knca-1 knock outs compared to wild type mice

3. Changes in circadian oscillation and amplitude of particular clock genes (Per2 and BMAL) were seen in knca-1 knockouts compared to controls

• Rama Maganti et al (Abstracts/AES/AAN 2012)
Summary

- The 24 hour expression of seizures in human epilepsy is usually not random
- The 24 pattern varies with epilepsy syndrome, with limbic seizures and some generalized seizures “ruled” by the CTS, and extratemporal cortical and some generalized seizures “ruled” by sleep/wake state
- Seizures and the epileptic lesion can affect clock function, but phenotypes of this disruption are not clear

Practical applications
Practical application 1: can timing aid in localization?

• 100 consecutive EMU patients

• For patients with seizures ≥ 3 for monitoring session, time of day of seizure aggregated into 0700-1900 (Day) and 1900-0700 (Night)

• Patients segregated into
  – Day majority (more day seizures > night)
  – Night majority (day seizures <= Night)

• Localization
  – Temporal
  – Nontemporal

  – Quigg, 1998 Annals

Can timing aid localization?: specificity/sensitivity

<table>
<thead>
<tr>
<th>Localization</th>
<th>Temporal</th>
<th>Nontemporal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majority of seizures: Dark</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>Majority of seizures: Light</td>
<td>45</td>
<td>15</td>
</tr>
</tbody>
</table>

• Sensitivity for temporal 70%
• Specificity for temporal 42%
• PPV 75%
• NPV 35%

Not stellar, but helpful
Practical application 2: timing of EEG may facilitate diagnosis of JME

- Compared standard awake EEG recording in the morning (0900) followed by an afternoon EEG (1500) in 29 patients with JME.
  - Morning: GEDs (+) in 20/29 patients
  - Afternoon: In 15 of the 20 GED(+), the afternoon recording was normal. Nine/29 patients had both morning and afternoon EEG recording normal.

Practical application 3: can state be manipulated to make seizures more helpful?

- SPECT scans: ictal SPECT tracer only available in day

- By sleep deprivation and allowing subsequent daytime sleep
  - Temporal lobe seizures should occur mainly during day, as they are circadianally mediated, and state should not have big effect
  - Extratemporal lobe seizures, being sleep-associated, should occur in day when SPECT tracer is available

- No data
Practical application 4: can timing of drug administration benefit patients with epilepsy? Chronopharmacotherapy

- It is well established that drug kinetics vary by time of day
  - Absorption
  - Distribution
  - Metabolism
  - Elimination

- Could we harness these changes to maximize effect and minimize morbidities with antiepileptic drug (AED) administration?

- This question has little data

Example: circadian influence on dose timing of ER theophylline for asthma. Amplitude of dose fluctuations varies with time of administration

*Levi Annu Rev Pharmacol Toxicol 2007*
Chronopharmacotherapy: circadian influences in drug administration/patient preferences

- One potential confounder: Patients may vary AED administration according to their particular phase preference “chronotype”

- Morningness/Eveningness scale (Horne-Ostberg)

- N=208 patients with epilepsy

- Timing of drugs varied with chronotype

  Hofstra et al, Epi Behav 2012

Does timing of AED dose affect pharmacokinetics?

- 16 male generalized epilepsy patients on phenytoin

- Randomized to two schedules
  - 8 subjects on single morning dose
  - 8 subjects on single evening doses
  - Repetitive serum levels

Evening dose patients had faster absorption, broader and lower peak serum concentrations, and reported less toxicities

Does timing of AED dose affect pharmacokinetics?

- 103 IGE patients with subtherapeutic phenytoin or carbamazepine randomized to two schedules
  - Equal bid dosing (ex: CBZ 200mg 2-2)
  - Evening weighted dosing (ex: CBZ 200mg 1-3)


Timing of AED dose affects seizure control in patients who have reliably timed seizures

- Retrospective n= 17 children with nocturnal or early morning seizures changed from
  - Equal dosing to
  - Weighted evening dosing (~2/3 in PM)
- 11/17 became sz free and 4 more had >70% reduction

- Guihoto L et al, Epi Behav 2011
Practical application: chronopharmacotherapy

- Several studies show that for patients with
  - Nocturnal or early morning/awakening seizure chronotype
  - Having daytime toxicities

  - That weighting AED BID administration to 2/3 of daily dose in the PM helps with toxicities and seizure control

Practical application 5: Recognition of chronotypes may help improve seizure control in medically refractory epilepsy

- Survey of 131 patients with epilepsy
- Insomnia severity index ≥ 10 = “insomnia”
- Seizure freedom over the past 4 weeks correlated with absence of insomnia (P<0.01) and with mean sleep time during free days (MSF)

Hypothesis: improving insomnia and sleep patterns may improve epilepsy

Data: Quigg unpublished
Summary

- The 24 hour expression of seizures in human epilepsy is usually not random
- The 24 pattern varies with epilepsy syndrome, with limbic seizures and some generalized seizures “ruled” by the CTS, and extratemporal cortical and some generalized seizures “ruled” by sleep/wake state
- Seizures and the epileptic lesion can affect clock function, but phenotypes of this disruption are not clear
- Shifting AED administration to evening-weighted in selected individuals may be helpful.