Sleep, Circadian Rhythms: Implications for Pediatric Epilepsy

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Presentation Outline

- Present an overview of
- Relationship between sleep and health in children,
- Sleep and wake concerns in children with seizures, with a focus on Dravet,
- Sleep disorders and their management to improve daytime functioning and seizure control.
Why are sleep and circadian rhythms important?

“If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process ever made.” A. Rechtschaffen

- Learning and memory
- Metabolism
- Cognitive and physical performance
- Neurological and mental health
- Physical health

- 50-70 million Americans have a chronic sleep disorder (IOM, 2006)
- Sleep disorders and deprivation are associated with many deleterious health consequences (IOM, 2006)
Sleep and Circadian Rhythm

Sleep Loss
Circadian dysregulation

Development

Sleep

Inflammation
Metabolism
Immune system
Autonomic function
Mood regulation
Neural function

Sleep and circadian rhythm disorders

HEALTH
Cognitive impairment
Neurological disorders (seizure)
Psychiatric disorders
Sleep/Wake Cycle
Circadian and Homeostatic Process

Homeostatic sleep drive

Circadian alerting signal

Awake

9 AM 3 PM 9 PM 3 AM 9 AM

Sleep

Wake

Wake propensity

Melatonin

Distribution of Sleep in Human Development

Adapted from Basics of Sleep Behavior, 1993
Sleep-Wake Cycle: A Dynamic Process

EEG Recordings

Awake

Stage 1 and REM

Stage 2

Stage 3

Stage 4

Sleep Across Lifespan

Circadian Rhythms
Daily Physiologic and Behavioral Patterns

- Noon (12:00): Best coordination
- 12:30: Fastest reaction time
- 01:00: Greatest cardiovascular efficiency and muscle strength
- 03:00: Highest body temperature
- 04:30: Deepest sleep
- 05:30: Lowest body temperature
- 07:00: Sharpest rise in BP
- 07:30: Melatonin secretion stops
- 08:00: Highest testosterone secretion
- 09:00: Morning Seizures
- 14:00: Bowel movements suppressed
- 17:00: Highest BP
- 18:00: Melatonin secretion starts
- 18:30: Highest BP
- 19:00: Highest body temperature
- 21:00: Deepest sleep
- 22:30: Nocturnal seizures
- 23:00: Bowel movements suppressed
- 24:00: Midnight

BP, blood pressure.
Timing of Seizures and Risk for SUDEP
Synchronizing Circadian Rhythms
Entrainment of the SCN and Peripheral Clocks

Melanopsin containing retinal ganglion cell-blue light

Information about the light environment

Peripheral clocks

Gl, gastrointestinal; PG, pineal gland; RHT, retinohypothalamic tract; SCN, suprachiasmatic nucleus; WBC, white blood cell.

Consequences of Sleep and Circadian Disruption

Learning
School
Mood and Performance
Behaviors Mental Health
Safety
Sleep Circadian
Health: Seizure
Family Relationships

Dewald et al, Sleep Med Rev, 2009
Disturbances in sleep and circadian rhythms increase neuronal irritability.

Improving circadian rhythms and sleep as targets for prevention and even disease modification.
Sleep and circadian abnormalities may be overlooked in children with epilepsy.

Sleep disturbance in children may lead to neurocognitive impairment, often in the form of attention deficit/hyperactivity, poor school performance, and poor memory.

**JME**, significant poor sleep quality (higher Epworth Sleepiness Scale). Ramachandraiah, *Epilepsy Beh* 2012; Krishnan, *Epilepsy Beh* 2012

**Primary generalized epilepsy**, longer N1 stage % & longer REM sleep latency and worse attention and emotional-behavioral symptoms. Maganti, *Epilepsia* 2005

**Benign Rolandic Epilepsy**, more daytime sleepiness, shorter sleep duration, and more frequent parasomnias than controls Tang, *J Child Neurol* 2011
Sleep and Circadian Rhythm Dysfunction in Dravet Syndrome

- Severe Myoclonic Epilepsy of Infancy
- Second year of life other seizure types begin to emerge.
- Most, but not all, patients test positive for SCN1A gene mutations.
- A higher incidence of SUDEP (sudden unexplained death in epilepsy).

Parents have observed that children with DS often experience difficulty falling asleep and staying asleep (Nolan et al., 2006).
Possible genetic basis of SCN1A function and sleep-wake disturbances

- **SCN1A** is coexpressed in brain regions that are important for sleep regulation (thalamic reticular nuclei, dorsal raphe nuclei, pedunculopontine, and laterodorsal tegmental nuclei) and seizure generation.

- **SCN1A** mutant mice show increased wakefulness and decreased NREM and REM sleep, potentially because of altered interactions of Nav1.1 channel with neurons of sleep-wake pathway. Papale LA, *Epilepsia* 2013

Han, S et al, *PNAS*, 2012
Six patients with genetically confirmed DS and complete polysomnography.

First report of polysomnographic variables in children with Dravet syndrome with analysis of both sleep macro- and microarchitecture, including CAP.
NREM sleep microarchitecture was, however, abnormal, with increased A1 subtype, somewhat resembling a tracé alternant pattern of neonates and possibly suggestive of cortical synaptic immaturity in Dravet syndrome.

- Frequent arousals
- Sleep apnea
How can we try to achieve this?
Sleep disorders– Common concerns

- “My child can’t fall asleep or stay asleep”
- “My child is too sleepy during the day”
- “My child does unusual things in sleep”
- “My child is overly active during the day” can also be a symptom of a sleep disorder
Evaluation of Sleeplessness

- Ask about bedtime, wake time, awakenings
- Is there a regular bedtime?
- Is there a bedtime routine?
- Are there any habits (stimulating activities before bed) that can be interfering with sleep?
- Sleep environment (temperature, light)
- Are there any medications that can be interfering with sleep?
- Is there evidence of a primary sleep disorder (obstructive sleep apnea, restless legs syndrome) contributing to poor sleep?
Evaluation of Sleep and circadian rhythms

- Polysomnography not generally indicated for insomnia
- Actigraphy and sleep diaries may be helpful in documenting bedtime/waketime and sleep phase
Behavioral Treatment

Bedtime resistance/difficulty falling asleep

- Bedtime routine: 30 minutes recommended
- Regular bedtime—be careful not too early!
- Avoidance of stimulating activities (TV, bright light) 1 hour before bedtime
- Getting enough exercise and **bright light** exposure during day
- Assess the sleeping environment: maybe door needs to be left open? A nightlight (**red or orange**) needs to be used?

- **Weighted blankets**

Courtesy: Beth Malow, MD
Timing of Bedtime is Important!

Resulting Pattern of Sleepiness and Alertness

- Homeostatic Drive
- Circadian Drive

Modified from Ferber R, Solving Your Child's Sleep Problems, 2006
Actogram of 14 year old with neurodevelopmental disorder before treatment

Actogram after Treatment (melatonin 5 mg at 8 pm)

1 month after melatonin treatment during vacation

6 months of treatment during summer vacation

5 year old with developmental delay treated with melatonin
Child with neurodevelopmental delay and epilepsy: difficulty falling asleep and daytime sleepiness
Sleep Wake Rhythm- Melatonin

- Melatonin has been used successfully to treat insomnia in typically developing children as well as those with neurodevelopmental disorders in retrospective and prospective studies, although double-blind placebo studies have not been carried out to date.
- Appealing to parents -- “dietary supplement” with few adverse effects
- Melatonin is not FDA-approved and purity of products not regulated
- Tasimelteon and Ramelteon (FDA-approved melatonin agonist) have not been approved for use in children
Obstructive Sleep Apnea in Children

- Often presents with loud snoring or noisy breathing—may not elicit history of frank apneas.
- Child is as likely to be hyperactive during the day as sleepy.
- Challenging to make diagnosis on history alone—screening questionnaires may assist but are not 100% sensitive or specific.
- Polysomnography is necessary to determine whether OSA is present (supported by American Academy of Pediatrics Clinical Practice Guideline).
- OSA provides a potential opportunity to treat associated symptomatology in typically developing children and those with neurodevelopmental disorders.
Sleep Problems and OSA

- In a cohort of > 800 children ages 2-14 seen in a general pediatrics clinic, inattention and hyperactivity were associated with increased daytime sleepiness and sleep disordered breathing. (Chervin et al, 2002)

- In a cohort of >3000 5-year-old children, those with sleep-disordered breathing were more likely to have daytime sleepiness and problem behaviors, including hyperactivity, inattention, and aggressiveness (Gottlieb et al, 2003)
Sleep Problems and Daytime Behavior

- Behavioral treatment of sleep problems in children with intellectual disabilities and challenging daytime behavior reduces parental stress, increases parents’ satisfaction with their own sleep, their child’s sleep, and heightens their sense of control and ability to cope with their child’s sleep (Wiggs and Stores, 2000).

- Short sleep duration has been associated with stereotypic behavior and social skills deficits (Schreck et al, 2004).

- Sleep problems have been related to repetitive behaviors (Gabriels et al, 2005).
Treatment of Sleep Apnea in Children

- Adenotonsillectomy is first-line treatment in children, BUT may not be appropriate in special populations.
- CPAP education/desensitization of the child and family can be very successful.
- Other options
  - Weight loss
  - Positional therapy
Children with neurodevelopmental disorders and seizures, particularly with intractable seizures are susceptible to sleep and circadian disorders.

Treatment of sleep disorders, in both typically developing children as well as those with neurodevelopmental disorders, can be viewed as an opportunity to positively influence daytime behaviors, and even the potential to modify seizure control and cognition.

Additional research will be needed to better understand the role of sleep and circadian rhythms as novel therapeutic approaches.
“Sleep is the golden chain that ties health and our bodies together”

Thomas Dekker, English Dramatist (1572-1632)