Clinical Sleep Research in the GCRC

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Presentation Goals
- To highlight the diversity of sleep research and its overlap with neurology, medicine, psychiatry, pediatrics, and other specialties
- To present examples of GCRC sleep research protocols/methodology of sleep research
- To stimulate discussion and invite questions on how others (you) can get involved

Personal Experience
- Fellowship-trained in epilepsy and sleep
- Early in my career, realized that sleep research was underexplored, and that the borderzones of sleep research and neurological disease were a fertile ground for understanding sleep and neurological diseases better
- GCRCs have provided the support to perform sleep studies at no charge to my career development awards

NIH Research on Sleep and Sleep Disorders Program Announcement (2-9-05)
- 13 different institutes of NIH represented
- Multiple scientific areas in sleep and sleep disorders need additional research
- Therapy for sleep disorders is suboptimal
- There are insufficient researchers addressing sleep science

NIH Research on Sleep and Sleep Disorders Program Announcement (2-9-05)
- Estimated 70 million people in the US suffer from sleep problems (50% have chronic sleep disorder)
- 30 million American adults have insomnia
- 18 million Americans have sleep apnea
- 250,000 Americans have narcolepsy
- 10-20% of adults have restless legs syndrome
- Each year, 100,000 accidents and 1500 traffic fatalities are related to drowsy driving
- Each year, sleep disorders, sleep deprivation, and excessive daytime sleepiness add approximately $16 billion annually to the cost of health care in the US and result in $50 billion annually in lost productivity
NIH Research on Sleep and Sleep Disorders Program Announcement (2-9-05)

- Sleep neurobiology: “understand the neuromodulatory role of hypocretin/orexin and the basic neurobiological processes that control sleep and wakefulness in narcolepsy and other conditions.”

Cataplexy in Narcoleptic Dobermans

Animal Model of Narcolepsy

- Narcoleptic colony of Doberman Pinschers was established in the 1970s
- Narcolepsy was transmitted as a single autosomal recessive gene with full penetrance in this breed
- In 1998, two independent groups (De Lecea, Sakurai) discovered a neuropeptide produced by lateral hypothalamic neurons:
  - hypocretin (hypothalamic peptide similar to secretin) and orexin (Greek for appetite)

Narcolepsy: Hypocretin/orexin

- 1999: Canine narcolepsy was attributed to a mutation of the gene coding for the hypocretin/orexin receptor (Lin)
- 2000: Reduced numbers of hypocretin/orexin neurons in postmortem brains of human narcoleptics (Thannickal)
- 2000: Low CSF hypocretin levels detected in human narcoleptics (Nishino)
- 2001: Low CSF and almost absent brain hypocretin content in canines (Ripley)

Hypocretin/orexin

- Produced in the lateral hypothalamus
- These lateral hypothalamic neurons project widely to many forebrain and brainstem regions that regulate sleep and alertness, as well as autonomic function and appetite regulation
- Hypocretins injected into lateral ventricle of animals raised blood pressure and heart rate, suggesting sympathetic stimulation
Narcolepsy: Hypocretin/orexin

Narcolepsy: Hypocretin/orexin
- Diurnal variation of cerebrospinal fluid hypocretin-1 (Orexin-A) levels in control and depressed subjects.
  Salomon RM, Ripley B, Kennedy JS, Johnson B, Schmidt D, Zeitzer JM, Nishino S, Mignot E. Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, Tennessee 37212
  Depressed subjects showed dampened diurnal variations of CSF hypocretin. Add sleep component?

NIH Research on Sleep and Sleep Disorders Program Announcement (2-9-05)

- Sleep deprivation: “Four to six hours of sleep each night results in a progressive, cumulative deterioration in neurobehavioral function including vigilance, neurocognitive performance, and mood. This reduction in performance is also associated with changes in cerebral activation during cognitive tasks. Physiologic changes also occur: insulin resistance, increased sympathetic activation, decreased immune system function.”

Sleep deprivation and fMRI

- Do acute and chronic sleep deprivation look similar in terms of performance on tasks of attention and higher cortical function?
- “Neural correlates of adaptation to sleep deprivation in obstructive sleep apnea - A pilot study”
- Grant proposal submitted to American Sleep Medicine Foundation (Dr. Kim Hutchison, Neurology)
- Sleep-deprive subjects in the GCRC and use daytime nap studies (MSLT) to gauge degree of sleep deprivation in relation to fMRI activation patterns on attentional and cognitive tasks.

Sleep deprivation is associated with decreased leptin levels and increased ghrelin levels which increase hunger and appetite (Spiegel, 2004)
Multiple Sleep Latency Test

- Overnight polysomnography the night prior to the MSLT is essential to document relatively normal sleep, exclude other sleep disorders.
- Subjects are given four–five naps (chances to fall asleep) starting 90 minutes to 3 hours after waking.
- Mean sleep latency (minutes to fall asleep on naps averaged together) and REM sleep (whether subject goes into REM sleep during a nap) are determined.
- Mean sleep latency < 8 minutes indicates daytime sleepiness.
- REM sleep on two or more naps suggests narcolepsy.

NIH Research on Sleep and Sleep Disorders Program Announcement (2-9-05)

- Sleep disordered breathing: “The consequences of obstructive sleep apnea have been increasingly defined over the last few years…”
Risk Factors, Symptoms, Outcomes, and Comorbid Conditions of Obstructive Sleep Apnea (OSA) in Adults

Young, JAMA, 2004

How underdiagnosed is OSA?

- Sample of 4,925 employed adults with a subset of 1,090 participants undergoing in-lab polysomnograms (PSGs).
- Questionnaire data on physician-diagnosed OSA were followed up to determine the prevalence of OSA.
- 93% of women and 82% of men with moderate to severe sleep apnea have not been clinically diagnosed.

Young, Sleep, 1997

Box 2. Identifiable Causes of Hypertension

Sleep apnea
- Drug-induced or drug-related
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease
- Chronic steroid therapy and Cushing syndrome
- Pheochromocytoma
- Coarctation of the aorta
- Thyroid or parathyroid disease


Sleep Problems and Daytime Behavior

- In children, sleep problems have been correlated with family or parental distress as well as with problematic daytime behavior (Patzold, 1998)
- 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, 2003)

Treating Sleep Apnea in Epilepsy

- “Effects of treating obstructive sleep apnea in epilepsy”
- ROI Multicenter Pilot Clinical Trial
- Vanderbilt, Michigan, University of North Carolina-Chapel Hill, Cleveland Clinic
- Goal is to work out design issues prior to embarking on a phase 3, definitive trial designed to answer the question:
- Does treating obstructive sleep apnea in patients with medically refractory seizures improves seizure frequency, daytime sleepiness, and health-related quality of life?

- Why is recognizing and treating sleep-related breathing disorders in epilepsy patients important?
  - Approximately 30 million people worldwide and 2 million Americans have epilepsy
  - Up to 30% of patients with epilepsy continue to have seizures despite appropriate therapy with antiepileptic drugs (Kwan and Brodie, 2000)
  - Sleep apnea may coexist with epilepsy and its treatment may improve seizure control, daytime sleepiness, QOL. These results are in case series or prospective trials. Randomized controlled studies have not yet been done.
Recruitment Period:
Adult patients with epilepsy surveyed. If screening, survey and evaluation + and meet study criteria, enter observational study.

Baseline Phase (8 weeks): 2 PSGs & MSLT at 6 wks

Treatment Phase
OSA + OSA -

Exit Study

Randomization

Continuous positive airway pressure (CPAP) works by using pressurized air to splint open the upper airway, preventing collapse during sleep.

A titration study in the sleep lab is followed by prescribing CPAP for home use.

End of Study PSG and MSLT

Extension of our GCRC protocol
- The highest prevalence of obstructive sleep apnea was seen in adults over age 40.
- The individuals most likely to comply with CPAP were adults over age 40.
- The causes of epilepsy in older adults are under intensive investigation. Could sleep apnea provoke later life seizures?
- "Obstructive Sleep Apnea in Older Adults with Epilepsy"
- Epilepsy Foundation of America Clinical Research Training Fellowship
- Dr. Annette Chihorek, Neurology

Only 40-60% of patients use CPAP every night when adherence is measured with usage meters.
Pediatrics: “The study of pediatric disorders such as congenital central hypoventilation syndrome and Rett syndrome has led to a better basic understanding of autonomic regulation and respiratory control…. recognition of the link between sleep disturbances and neurobehavioral disorders in childhood… has major public health implications for both the treatment and prevention of psychiatric co-morbidity.”

Circadian biology: “A growing number of “clock genes” play a role in circadian timing… the role of melatonin to treat sleep disorders needs to be better defined…”

Objectives

Autism: A spectrum of neurobehavioral developmental disorders characterized by deficits in social interaction and communication, with repetitive behavior patterns and a limited repertoire of interests

The long-range goals of this research are:

- To define the causes of sleep disorders in children with autism spectrum disorders
- To measure the impact of treating these disorders on daytime behaviors

Autism and Sleep

Is sleep abnormal in individuals with autism spectrum disorders– what is the evidence?

- Neurobiological abnormalities have been described in autism, including alterations in neurotransmitters and hormones involved in sleep regulation (serotonin, melatonin)
- A variety of sleep abnormalities have been reported in children with autism using:
  - Questionnaires given to parents of children with autism
  - Polysomnographic (sleep) studies

Autism and Sleep

- **Insomnia** is the primary sleep concern in surveys completed by parents of children with autism:
  - Later bedtime and prolonged time to fall asleep
  - Early morning wake time
  - Frequent arousals during the sleep period
  - Cause??? Varies by investigative group!
    - Circadian rhythm disorder (delayed sleep phase)
    - Poor sleep habits/sleep onset association disorder
    - Obstructive sleep apnea
    - Epileptic seizures
    - Parental overconcern???
Interdisciplinary Discovery Grant Project

- Hypothesis: Disordered sleep on polysomnography (PSG) is more common in children with autism whose parents report sleep concerns.
- Three age-matched comparison groups:
  - Children with autism with parental sleep concerns (moderate to severe)
  - Children with autism without parental sleep concerns (none or mild)
  - Children without autism and without parental sleep concerns

Study Criteria

Inclusion Criteria:
- Ages 4-10
- Diagnosis of autism by history and ADOS
- Average cognitive skills on the PPVT
- Able to cooperate with polysomnography

Exclusion Criteria:
- Mental retardation
- Epilepsy
- Psychotropic medications

Actigraphy: movement quantifiers

CSHQ = Child Sleep Habits Questionnaire
PCQ = Parental Concerns Questionnaire
CBCL = Child Behavior Checklist
FISH = Family Inventory of Sleep Habits

Preliminary findings

- Parents of 43 children with autism surveyed
- 42% of parents reported moderate to severe sleep concerns.
- Compared to those without parental sleep concerns, these children showed a significantly shorter sleep duration on the Child Sleep Habits Questionnaire.
Preliminary findings
- Compared to those without parental sleep concerns, children with parental sleep concerns showed significant differences on the Child Behavior Scale Checklist in dimensions related to:
  - Attention deficit/hyperactivity
  - Affective disorders
  - Anxiety
  - Emotional reactivity
  - Being withdrawn
  - Aggression

Preliminary findings
- In-hospital sleep studies have been completed and analyzed in:
  - 3 children with autism and sleep concerns
  - 4 children with autism without sleep concerns
  - Sleep efficiency (time asleep/time in bed) was 93% in the children without parental sleep concerns and 72% in the children with parental sleep concerns
  - Sleep latency (time to fall asleep) was 12 minutes in the children without parental sleep concerns and 107 minutes in the children with parental sleep concerns
  - Sleep logs and sleep history mirrored sleep study results in these children

Preliminary outcomes
- One of the three children with sleep concerns had obstructive sleep apnea, and showed frequent arousals as well as poor sleep efficiency and time to fall asleep.
- She recently underwent tonsillectomy, with her mother reporting fewer arousals from sleep and more focused behavior during the day.

Preliminary findings
- “The change in my daughter has been absolutely remarkable, and I’m hoping the next few months will bring even more improvements. Her interest in everything and everyone around her has greatly increased. She sleeps soundly through the night and wakes happy in the morning… the length of time she can follow directions has increased.”
- “She also tolerates longer social interaction, with a co-worker of mine who observed her recently mentioning ‘My, I sure am getting much more unsolicited conversation.’”

Next Steps
- Tease out the physiological and behavioral components of insomnia in a group of children with autism spectrum disorders
  - Poor sleep habits?
  - Impaired secretion of melatonin?
  - Genetic factors, including circadian-related genes?
  - Coexisting sleep disorders (e.g., sleep apnea)?
- Perform a clinical trial looking at the effects of behavioral and pharmacological interventions (melatonin???) on sleep and behavior in children with autism and insomnia

Let’s talk about YOUR ideas for a GCRC sleep protocol!