Overview of Normal Sleep Physiology

Kiran Maski, MD
Harvard Medical School
Boston Children’s Hospital

Sleep Architecture

Sleep onset
10-30 minutes

Circadian Features of REM sleep

Development of Normal Sleep Rhythms

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Sleep</th>
<th>Naps</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 y</td>
<td>11.25 hours</td>
<td>1-&gt;0</td>
</tr>
<tr>
<td>6 y</td>
<td>10.5 hours</td>
<td>0</td>
</tr>
<tr>
<td>10 y</td>
<td>10 hours</td>
<td>0</td>
</tr>
<tr>
<td>16 y</td>
<td>9.13</td>
<td>0</td>
</tr>
</tbody>
</table>

Hypersomnia

- At least 3 months of daytime sleepiness defined by the inability to stay awake and alert during major waking episodes during the day resulting in an irresistible need for sleep or unintended lapses into drowsiness or sleep
- More likely to occur in sedentary, boring, monotonous situations
- Most aware of sleepiness though rarely “sleep attacks” occur with no prodrome
- +/- accompanied by increases in total daily amount of sleep
- +/- restorative feelings about sleep
- Children may paradoxically present with hyperactivity, inattention, emotional lability

International Classification of Sleep Disorders 3rd Ed, 2013.
CNS Hypersomnia

Chronic (> 3 months)

Primary

Narcolepsy

Hypersomnia due to a medical condition

Acquired

Genetics/ Metabolic

Secondary

Hypersomnia due to medication

Hypersomnia associated with psychiatric disorder

Recurrent or periodic (once per 12-18 mo)

Kleine Levin syndrome

Menstrual related

* Excludes hypersomnia due to insufficient sleep or a primary sleep disorder
A to Zzz’s: CNS Hypersomnia conditions in children

Part 2 – Clinical update on hypersomnia

Shelly Weiss, MD
University of Toronto

Objectives

Primary vs. Secondary Causes of Hypersomnia

Diagnostic evaluation of hypersomnia

Advances in understanding of hypersomnia after TBI

What is the most common cause of pediatric hypersomnia?

Insufficient Sleep

Excessive Daytime Sleepiness
A practical approach

Conditions of EDS with Increased Need for Sleep

Primary
Due to a central cause

Secondary
Not due to a central cause
Primary vs. Secondary Hypersomnia

<table>
<thead>
<tr>
<th>Primary Due to a central cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcolepsy</td>
</tr>
<tr>
<td>Idiopathic hypersomnia</td>
</tr>
<tr>
<td>Recurrent hypersomnia (Klein Levin Syndrome)</td>
</tr>
<tr>
<td>Inherited disorders (e.g. Niemann Pick C)</td>
</tr>
<tr>
<td>Hypothalamic lesions</td>
</tr>
<tr>
<td>Traumatic Brain Injury</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Not due to a central cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>M.S.</td>
</tr>
<tr>
<td>Drug related</td>
</tr>
<tr>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Other sleep disorders (e.g. insomnia, O.S.A., RLS)</td>
</tr>
<tr>
<td>+ + +</td>
</tr>
</tbody>
</table>

Primary Hypersomnia
- Narcolepsy
- Idiopathic hypersomnia
- Recurrent hypersomnia (Klein Levin Syndrome)
- Inherited disorders (e.g. Niemann Pick C)
- Hypothalamic lesions
- Traumatic Brain Injury

Secondary Hypersomnia
- Not due to a central cause
- Depression
- M.S.
- Drug related
- Alcohol abuse
- Other sleep disorders (e.g. insomnia, O.S.A., RLS)
- + + +

To make things a bit more complicated: how the sleep community classifies hypersomnias

Disorders of Hypersomnia

- Narcolepsy Type 1
- Narcolepsy Type 2
- Idiopathic Hypersomnia
- Kleine-Levin Syndrome
- Hypersomnia due to a Medical Disorder
- Hypersomnia due to a Medication or Substance
- Hypersomnia Associated with a Psychiatric Disorder
- Insufficient Sleep Syndrome

American Academy of Sleep Medicine, 2014

Kleine Levin Syndrome: Periodic hypersomnia

- Adolescents, male:female = 4:1
- 10 -14 days of hypersomnolence, with sleep 18 - 20 hours /day
- Feelings of depersonalization, mood disturbance, compulsive hyperphagia, and hypersexual behavior
- Intervening 2 - 4 months of normal alertness and behavior
- Binge eating may be associated with a 2-5 kg weight gain

Diagnosis and Treatment

- PSG: (sleepy periods) shows dec. sleep efficiency, shortened latency to REM sleep, dec. time in N3
- MSLT: shortened mean sleep latency (5-10 min.); No SOREMPs
- Episodes of sleepiness gradually diminish over time
- Usually resolve over 5 to years or evolve into classic depression,
- Disturbance of hypothalamic function hypothesized
- ? autoimmune etiology associated with histocompatibility antigen DQB1*0201 and the occasional precipitation after systemic infections,
- Treatment: difficult. Modafinil may be useful
Objective 2

Diagnostic evaluation of hypersomnia

Subjective Measures

- Sleep logs/diaries
- Sleep scales
- Sleep questionnaires

Sleep Diaries

Pro
- Simple, cost effective
- Variety are available
- Completed by parent (or adolescent) every 24 hours
- Typically used for one week

Con
- Reports by parent or adolescent may not be accurate

Kushnir J. Jnl of Clin Sleep Med 9 (11) 2013
Aora T. Plos ONE 8(8) 2013

Sleep scales/sleep questionnaires

- Many questionnaires available to screen for sleep disorders
- Children Sleep Habits Questionnaire (CSHQ) used widely in research
- For a review of sleep questionnaires:
  - Spruyt, K., & Gozal, D. (2011). Development of pediatric sleep questionnaires as diagnostic or epidemiological tools: a brief review of dos and don’ts. & Pediatric sleep questionnaires as diagnostic or epidemiological tools: a review of currently available instruments. Sleep Medicine Reviews, 15(1)

Epworth Sleepiness Scale- Children

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, think about how they would have affected you. Use the following scale to choose the most appropriate number for each situation.

0=would never doze or sleep
1=slight chance of dozing or sleeping
2= moderate chance of dozing or sleeping
3=high chance of dozing or sleeping.
ESS activities

Circle the most appropriate number for each situation:

1. Sitting and reading
2. Watching television
3. Sitting inactive in a public place (for example, a movie theater or classroom)
4. As a passenger in a car for an hour without a break
5. Lying down to rest in the afternoon when circumstances permit
6. Sitting and talking to someone
7. Sitting quietly after lunch
8. Doing homework or taking a test

Pros/Cons: Sleep Questionnaires

Advantages
- Brief, easily administered
- Low patient burden

Disadvantages
- Recall bias
- Few questionnaires rigorously evaluated for psychometric properties
- Limited usefulness in patients who are unable to self-report reliably
- Limited validity compared with PSG
- Reports by parent or adolescent may not be accurate

Kushner J. J Clin Sleep Med 9 (11) 2013
Arca R. Plos ONE 8(8) 2013

Epworth Sleepiness Scale - Children

Adapted from ESS (adults)
John MW. Sleep 1991 (50-55)
Not validated in children

Score: 0-9 WNL
> 10 Sleepy
> 18 Very Sleepy

Objectives Measures

- Actigraphy
- Polysomnography
- Multiple sleep latency test (MSLT)
- Multiple wake test (MWT)

Actigraphy

Monitor movements over extended time – translates to sleep-wake scores based on computerized scoring algorithm
Cost-effective method
Recommended to use with complementary objective and subjective methods
Specific devices and algorithms have difference validity
Extended monitoring (3 days or longer) increases reliability

Sadik A. Sleep Medicine Reviews 15 (2011)

Pros/Cons: Actigraphy

Advantages
- Provides objective information about daily variability and sleep quality
- Records information in the home sleep environment
- Not influenced by recall bias or memory impairments
- Lower cost than PSG

Disadvantages
- Limited usefulness in assessment of sleep onset latency
- Low specificity in detecting wakefulness within sleep periods reported with certain devices or samples (Sadik 2013)
- Need parent to complete sleep diaries concurrently to enhance quality of information
- Children (especially with NDD) may have difficulties complying with actigraphy
Polysomnography

Definitions

• PSG - overnight in-laboratory polysomnography
• MSLT - multiple sleep latency test
• MWT - multiple wake test

Pros/Cons: PSG

Advantages
• Gold standard objective assessment of sleep

Disadvantages
• Inconvenient for parent and may necessitate missing work
• High cost
• Can lead to a "first night effect" phenomenon
• May be difficult or not possible to have a child to cooperate to obtain a representative night’s sleep

Other diagnostic tests for hypersomnia

• Laboratory evaluation/ Neuroimaging/EEG: to rule out secondary causes
• CSF Hypocretin-1 levels and HLA subtypes

To be discussed in Part 3: Dr. Kotagal
Objective 3

Advances in understanding of hypersomnia after TBI

Limitations in studies of EDS in pediatric TBI

• Studies have small sample sizes
• No pre-injury data
• Mainly based on subjective reports

Note: Next 3 slides adapted from Hung R. CNSF Conference June 2014

All sleep disorders following TBI

• Hypersomnia (related to severity of TBI)
• Excessive daytime sleepiness
• Insomnia
• Circadian Rhythm Disorders
• Sleep related breathing disorders

Many possible causes of hypersomnia after TBI

• Damage to areas of brain involved in regulation of sleep-wake cycle or circadian rhythm
  • E.g. Loss of hypocretin neurons or decreased melatonin production
  • Sleep Apnea – central/obstructive/mixed
  • Chronic pain
  • Seizures
  • Psychosocial/Psychological (depression, anxiety)
  • Side effects of medications

What do we know about pediatric sleep post traumatic brain injury?

• A systematic review of the literature identifies gaps in research and knowledge
• Manuscript prepared for publication


<table>
<thead>
<tr>
<th>Study</th>
<th>Objectives</th>
<th>Design</th>
<th>Age No. Severity</th>
<th>Follow up</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xavier 2011</td>
<td>ID in males and females with sleep-related concussions</td>
<td>Prospective cohort: No control. Assessed: Event-based surveillance system.</td>
<td>Mean age: 16yrs No: 812 Not indicated</td>
<td>1 year with weekly sleepers</td>
<td>Shortened sleep duration reported more commonly in females (17%) than in males (9%).</td>
</tr>
<tr>
<td>Thomas 2011</td>
<td>Comparison of sleep quantitative assessment immediately following TBI with later evaluation</td>
<td>Prospective cohort: No control. Computer assessment and Telephone interview</td>
<td>11-17 yrs No: 44 Mild 34, 24, 6, 36, 36</td>
<td>24% EDS in 35.8%</td>
<td></td>
</tr>
<tr>
<td>Thomas 2012</td>
<td>ID and association with functional outcomes</td>
<td>Prospective cohort: Orthopedic outcomes PathGL</td>
<td>2.17 yrs No: 79 TBI 187 controls mild-severe</td>
<td>Baseline, 3mos, 12mos, 24mos</td>
<td>Moderate to severe TBI and SCI</td>
</tr>
<tr>
<td>Odena 2013</td>
<td>Association of sleep disorders in survivors</td>
<td>Cross-sectional study Parent/youths sleep measures</td>
<td>12-18 years No: 182 mild-severe Within 4 months of injury</td>
<td>EDS in mild-severe TBI patients but not youth report</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

Studies consistently show increased EDS, associated with more severe TBI

Methodology differs markedly in studies

More research is needed in this area

Patterns of Sleepiness in Patients with TBI

- Extension of sleep time
  - Duration of sleep increased from 7.3 hours to 10.8 hours post TBI in adult cohort
  - Higher amounts of slow wave sleep also described (13% vs 20%)

- Insomnia
  - In retrospective studies, 40-50% report insomnia and daytime fatigue and sleepiness (Sommerauer et al. Neurology 2000, Brunet et al. Sleep Med 2006)
  - May be associated with higher depression and anxiety co-morbidities

- Circadian disruptions
  - 36% of patients in one cohort: irregula circadian rhythms/Delayed sleep phase (Pilcher et al. Archives of Neurology 2007)
  - Lower dim light melatonin onset in TBI patients compared to controls (Ekelund et al. Neurology 2006)

Treatment for Hypersomnia post TBI in Adults

- Modafinil
  - Class 1 evidence: 100-200 mg improves post-traumatic EDS compared to placebo in trial of 20 adult patients based on ESS scores and MWT at 6 weeks
    - No significant improvement in fatigue levels
    - Safe and well tolerated

- Methylphenidate/Dexamphetamine
  - Class 1: methylphenidate 5-20 mg/day improved daytime sleepiness on ESS in 4 week double blind study comparing stimulated to placebo (Brunet et al. Neurology 2006)
    - Stimulants better tolerated than sertraline and had significant effect on depressive symptoms and cognitive testing

- Blue light
  - Class 1: short wave length blue light therapy (39.5 lux) 45 minutes on waking for 4 weeks resulted in significant reduction in sleepiness and fatigue at 4 and 8 weeks after 10% compared to yellow light and no light (Sommerauer et al. Sleep Med Rev 2006)