Measurement of Circadian Rhythm and Sleepiness in Children

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Outline

- Circadian Rhythm
  - Cortisol Measurement
  - Melatonin Measurement
- Excessive Daytime Sleepiness
  - Subjective Assessment
  - Objective Assessment
Circadian Rhythm

- Sleep Homeostatic drive (Sleep Load)
- Circadian alerting signal

Alertness level

Wake

Time

9 AM  3 PM  9 PM  3 AM  9 AM

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Hormones Implicated in Circadian Rhythm

- Hypothalamic-Pituitary-Adrenal (HPA) Axis
  - Dysregulation implicated in sleep disturbance
- Cortisol
  - Promotes wakefulness
  - Also responsive to stress
- Melatonin
  - Promotes sleep
  - Dim Light Melatonin Onset (DLMO)
- Measurement almost exclusively for research purposes
Circadian Pattern of Cortisol

- Higher levels upon awakening and early afternoon associated with poorer sleep in infants and children

El-Sheikh et al., 2008; Hartzinger et al., 2008
* Integrative Therapeutics
Cortisol Measurement

- Need to collect at least 3 samples to evaluate diurnal rhythm
  - Within 30 minutes of waking
  - Mid-afternoon
  - 30 minutes prior to bedtime
- Helpful to have at least 2 days
- May collect in response to stress if variable of interest
  - Pre-exposure
  - Post-exposure: 20, 40, 120 minutes

Corbett et al., 2006; Kiel et al., 2015
Melatonin Secretion

- Suprachiasmatic nuclei (SCN) of the hypothalamus
- Responsive to light-dark cues
  - Onset in response to dim light
- High levels at night
- Low levels during day
- Need at least 4-5 samples
  - If have luxury of a lab, can obtain 24 hour sampling every 2-3 hours

Arendt, 2006; Cardinali & Pevet, 1998; Novakova et al., 2011; Praninskiene et al., 2012
Melatonin Rhythmicity

Praninskiene et al., 2012
Cortisol and Melatonin

* Clintrinsic
Sample Collection Options

- Serum
  - Not as well tolerated by children

- Urine

- Saliva
  - Most tolerated by children
  - Methodological challenges

- Urinary and salivary melatonin levels significantly correlated
  - Urinary levels show peak later than salivary levels
  - High intraindividual variation
  - Urinary samples with higher rates of problems

Praninskiene et al., 2012
Urinary Secretion

- Overnight Urinary 6-Sulfatoxymelatonin (6-SM)
  - Primary melatonin metabolite excreted in urine
- Collect first morning urine
  - Only effective in children without nocturnal enuresis
  - Only useful for overall melatonin levels
  - Not helpful for determining circadian rhythmicity
- Collect urine every 3 hours to determine rhythmicity
  - Requires waking child

Leu et al., 2011; Praninskiene et al., 2012
Salivary Collection

- Need multiple samples at set times to determine DLMO and circadian rhythmicity of cortisol and melatonin
- Stimulate saliva
  - Rinse mouth with water
  - Chew gum
- May use Trackcap
- Helpful to avoid eating, drinking, brushing teeth just before saliva collection.
- Can use cotton tube or straw to collect into tube
How to collect a saliva sample

Nancy West, MSN, RN
1. Rinse your mouth with water 10 minutes before you start.
2. Choose the right tube. Take the cap off.

- Sample 1 yellow top tube
- Sample 2 red top tube
- Sample 3 green top tube
- Sample 4 blue top tube
- Sample 5 white top tube
3. Allow saliva to pool in your mouth. It may help you to imagine eating your favorite foods.
4. Hold the straw so that it is in the tube.
5. Tilt your head forward and drool down the straw.
6. Repeat until you have filled the tube to the black line. Put the cap back on the tube.
7. Put the tube in a zip lock bag and store in the freezer.
Salivary Melatonin Collection Log

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Date collected</th>
<th>Time collected</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 YELLOW (3 hours before usual bedtime)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 RED (2 hours before usual bedtime)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 GREEN (1 hour before usual bedtime)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 BLUE (Usual bedtime)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 WHITE (1 hour after usual bedtime)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Thank you for helping us learn!
Take Home Messages

- No clear clinical use of circadian evaluation of cortisol and melatonin
  - Would be nice, particularly for melatonin because of prescription of exogenous melatonin
- Have choice of serum, urine, or saliva sampling
  - Saliva may be most tolerated
  - Data collection can be challenging
- If want a true circadian rhythm evaluation of hormone, need to awaken child throughout the night
  - Salivary collections can be timed to identify just onset and peaks of hormone secretion
Excessive Daytime Sleepiness
Excessive Daytime Sleepiness

- Differentiated from fatigue
  - Though may be described as “tired”
- Propensity to fall asleep
- Difficulty remaining awake for activities
- Increase in napping
- Longer sleep duration
- Difficulty waking in the morning
- May vary from mild to severe
- May be caused by insufficient sleep or hypersomnia/narcolepsy

Fallone et al., (2002)
Assessment of Sleepiness

Subjective
- Modified Epworth Sleepiness Scale
- Children’s Report of Sleep Patterns (CRSP) Sleepiness Scale
- Pediatric Sleep Questionnaire Sleepiness Scale (PSQ-SS)
- Research or clinical purposes

Objective
- Multiple Sleep Latency Test
- Research or clinical purposes
Epworth Sleepiness Scale (Modified)

**SCORE**
- 0 = no chance of dozing
- 1 = slight chance of dozing
- 2 = moderate chance of dozing
- 3 = high chance of dozing

**SITUATION**
- Sitting and reading
- Watching TV
- Sitting inactive in a public place (e.g. a theater or meeting)
- As a passenger in a car for an hour without a break
- Lying down to rest in the afternoon when circumstances permit
- Sitting and talking to someone
- Sitting quietly after a lunch
- In a car, while stopped for a few minutes in traffic
Modified Epworth

- Clinical indication—concerns related to daytime sleepiness
  - Not diagnostic
- Scores above 10 indicative of sleepiness in adults
- Can be administered to caregivers or children themselves (if 6 years of age and older)
  - Good agreement between parent-child in validation sample
  - Fair to poor agreement between parent and child (especially adolescents) in cancer and cancer survivor samples

Brimeyer,…Crabtree, 2015 in press; Graef,…Crabtree, 2015; Melendres et al., 2004
Modified Epworth

- Significantly discriminates samples with sleep-disordered breathing than controls
  - Does not correspond to severity of sleep-disordered breathing
  - Mean scores below 10 (typically 8)
- Score of 8 and above may be best cut-off (29% sensitivity; 91% specificity in children with OSA), but still low sensitivity
- Does not show good sensitivity (44%) or specificity (77%) in relation to objective measures of sleepiness in children with brain tumors

Chan et al., 2009; Crabtree et al., 2015 in press; Melendres et al., 2004
Modified Epworth vs. MSLT

Crabtree et al., 2015 in press
Children’s Report of Sleep Patterns—Sleepiness Scale

- Child self-report ages 8-18
- Clinical indication—desire self-report of sleep patterns
  - Sleepiness scale when have concerns about daytime sleepiness
  - Not diagnostic

Meltzer et al., 2012
CRSP-S

- 5 item scale
- How often do you feel sleepy or fall asleep when you are:
  - eating,
  - talking with someone else
  - at school
  - playing and riding in the car or bus for a short time (less than 20 min)
- 5-point Likert scale

Meltzer et al., 2012
CRSP-S

- Distinguishes clinical from non-clinical samples
- Positive correlation with parent-reported sleepiness
  - Though not 1:1 correspondence
  - Highlights importance of self-report
- High self-reported sleepiness associated with other self- and parent-reported sleep disturbances.

Meltzer et al., 2012
Pediatric Sleep Questionnaire—Sleepiness Scale

- 4 items
- Scored Yes, No, I don’t know
- Parent report
- Does your child wake up feeling unrefreshed in the morning?
- Does your child have a problem with sleepiness during the day?
- Does your child appear sleepy during the day according to teacher/other caregiver comments?
- Is your child hard to wake up in the morning?

Cut-off of 0.33

Chervin et al., 2000
PSQ-SS

- Significantly differentiates children ages 5-12.9 with OSA from controls
- Weak negative correlation with MSLT Mean Sleep Onset Latency

Chervin et al., 2006
Multiple Sleep Latency Testing

- Clinical indication—suspected narcolepsy in children 5 years of age and older
  - Option—concerns related to hypersomnia not associated with narcolepsy
- Diagnostic tool
- Should be preceded by nocturnal polysomnography
  - Can be modified to 30 minutes in children
- EEG-recorded sleep onset
- EEG, EOG, EMG recorded sleep staging
Your Multiple Sleep Latency Test (MSLT)
What to expect

1. Lights on
2. Patient awake
3. Electrodes reapplied
4. 20 minute nap
5. Patient awake
6. 20 minute nap
7. Patient eats lunch
8. 20 minute nap
9. Patient leaves
Interpretation of MSLT

- Mean Sleep Onset Latency (SOL) of 8-10 minutes indicative of narcolepsy/hypersomnia
  - Most with narcolepsy will have mean SOL of 8 minutes
  - Hypersomnia associated with “borderline” mean SOL of 10 minutes
- 2 or more Sleep-onset REM (SOREM) periods indicative of narcolepsy
  - Many adolescents have 1 SOREM
- May be useful in determining response to treatment for narcolepsy

Aurora et al., 2012
Take Home Points

- Have several questionnaire options for self- or parent-report of sleepiness
  - All should be used as screeners rather than diagnostic tools
  - None have excellent sensitivity/specificity in relation to gold standard
  - Self-report is essential if child old enough to report
- MSLT is gold standard
  - Objective documentation of sleepiness
  - Need NPSG first
  - Costly, requires sleep lab equipment
Questions?

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References


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