Sleep in Children with CHARGE Syndrome
Susan Wiley, MD, Cincinnati Children's Hospital Medical Center
Christine Heubi, MD, Cincinnati Children's Hospital Medical Center

Presenter Information
Susan Wiley is a developmental-behavioral pediatrician with clinical and research interests in children who are Deaf/Hard of Hearing with complex developmental and medical needs. She is the co-director of the CHARGE clinic at Cincinnati Children’s Hospital Medical Center. She is a member of the cochlear implant team and has worked with the Ohio Center for DeafBlind Education and American Academy of Pediatrics on topics related to children who are Deaf/HH and Deaf/HH Plus.

Christine Heubi is a pediatric ear, nose, and throat physician with board certification in sleep medicine and otolaryngology. She takes care of children with upper airway obstruction, tracheostomy tube dependence, obstructive sleep apnea, insomnia, and circadian rhythm disorders. Her research is focused on sleep disorders in special populations, including children with CHARGE syndrome. She works in collaboration with Dr. Susan Wiley, co-chairperson of the CHARGE clinic at Cincinnati Children’s Hospital, to improve the quality of life in children with CHARGE syndrome. Most recently, she and Dr. Wiley presented at the annual CHARGE meeting held in Cincinnati in July, 2018 for both professionals and parents.

Presentation Abstract
Sleep problems in CHARGE syndrome are estimated to occur in 59% of patients, and can be related to anxiety and behavioral concerns. Limited research has been performed, with parental survey as the primary source of reported issues. Caregiver well-being has been found to be affected by sleep problems in children with CHARGE, and recommendations need to be made once the underlying issue is determined: medical issues (night time feedings or treatments, obstructive sleep apnea, pain), visual impairment, hearing loss, or environmental factors. Both behavioral and environmental interventions can be successful, however, further evaluation and treatment may be necessary. Light therapy and supplementation with melatonin, or other medication, can lead to clinical improvement in certain patients. In other patients, attention is focused on evaluation and management of upper airway obstruction. Sleep endoscopy and cineMRI are employed for diagnosis of the site of obstruction; treatment includes surgery, positive airway pressure (PAP) therapy, and/or medication. Case presentations will be used as examples for the work-up and management of children with CHARGE who have sleep problems.

Learning Objectives
- Identify sleep problems in children with CHARGE syndrome.
- Describe the work-up and management of sleep disorders in children with CHARGE syndrome.
- Discuss special considerations in this population including the impact of visual impairment, circadian rhythm disorders, and sleep disordered breathing.
Sleep issues in CHARGE Syndrome

- Recognize that sleep issues are common (>57%) in CHARGE and can be multifactorial
- Implement systematic sleep history
- Recognize when further studies are indicated
- Discussion of sleep medications
  – not based on evidence, but on experience and understanding of how medications typically work

Sleep History

- Bed time and wake time
  – Ask about routine to determine sleep hygiene
  – Use of electronics and/or stimulating behaviors
  – Daytime sleepiness and napping
  – School performance
  – Mood
- Sleep environment
  – Medical equipment
  – Darkness level
- Sleep disordered breathing
  – Snoring, choking/gasping, snorting, apnea, pauses
- Restless sleep
  – Daytime symptoms of achy legs
- Parasomnias (sleep talking, walking, sleep behaviors)
  – Important in consideration of sleep medications

Why so common? Many potential risks for poor sleep in children with CHARGE

Child Factors:
- Atypical circadian rhythms
  – Melatonin production?
  – Light exposure from hospital environment/nursing care?
- Medical disruptions
  – Health issues, frequent suctioning, night-time feedings, intercurrent illnesses
  – Pain
- Difficulties with self-regulation, self-soothing, sleep onset

Environmental factors:
- Sleep environment
  – Lack of consistent routines
- Variability in caregivers night-time routines (night nursing)
- Medical factors
  – Side effects of medications

Chronobiology

- Sleep logs for 2 weeks
  – Total sleep time
  – Identify sleep phase disorder
  – Delayed sleep phase disorder
  – Free running circadian disorder
- Actigraphy can also be employed

Circadian rhythm disorders

- Free running circadian disorder
- Delayed sleep phase disorder
  – Later bed time
  – Normal propensity as adolescent
  – Can be managed with light and melatonin
- Time spent in ICU/hospital
- Autonomic dysregulation
Impact of Visual Impairment on Sleep

- Sleep mediated by
  - Process S: DRIVE for sleep
  - Process C: Circadian rhythm “clock”
    - Modulated in part by light
    - Light suppresses melatonin
- Blind individuals report more sleep disturbances than sighted individuals
  - Lack of entrainment by light
  - Abnormal timing of melatonin release
  - Greater incidence of a free-running circadian rhythm

Light exposure

- Newer evidence that some blind individuals retain cells for photic circadian entrainment
  - 16 visually blind individuals exposed to bright light and melatonin measured for suppression
    - 50% were responsive to light
- Why is this important?
  - Important not to disregard sleep hygiene instructions in regard to light exposure
    - Black out shades in bedrooms
    - Early morning light exposure for 30 minutes
      - Natural light preferred
    - In some cases, light tones are helpful
    - Discontinue device and TV at least 1 hour before bedtime (blue light)
    - Keep electronics out of bedroom


Sleep Disordered Breathing

- ENT/sleep referral vs. Polysomnography (PSG)
  - Snoring >3 days per week
  - Associated with any signs or symptoms
- Adenotonsillectomy is first line
- HST is not recommended for children
- Home oximetry is not reliable
  - Post T&A symptoms or pre-decanulation
- PSG
  - For sleep study, daytime to 2:50 AM
- Management of persistent OSA
  - CPAP should be considered
  - CineMRI and/or DISE (Drug Induced Sleep Endoscopy)


Evaluation for site of obstruction

- Nasal
- Nasopharyngeal
- Retropalatal
- Retroglossal
- Hypopharyngeal
- Supraglottis/laryngeal

Value of DISE & cineMRI

- Sedation is similar to natural sleep state
Periodic Limb Movements of Sleep (PLMs)

- Treatment indicated if index > 5 per hour with history of restless sleep
  - Some night to night variability
- Check CBC, ferritin
  - If ferritin < 50, start ferrous sulfate 3 mg/kg/day divided BID (max 2 tabs per day)
  - Re-check labs in 3-4 months
- Other treatment options:
  - Clonazepam (low dose)
  - Melatonin
  - Can also consider gabapentin

Psychotropic medication use in CHARGE

- Survey of families, 87 respondents
- Authors linked medication to reported diagnoses
- Caveats:
  - Often medications are used for target behaviors rather than distinct diagnoses
  - Sleep disturbances were not specifically queried
- Medication Use:
  - Clonidine in 11/87 (12%)
  - Benzodiazepine class in 3/87 (3.5%)
  - Sleep medications such as Mirtazapine and trazodone were not reported

Sleep Medications

### Sleep Medications

- Most without FDA approval for sleep or for children

<table>
<thead>
<tr>
<th>Class</th>
<th>Dosing Considerations</th>
<th>Potential Side Effects</th>
<th>Adverse Reactions</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin</td>
<td>Hormone 1 mg at dinner (low dose to prime the internal clock) 2.5-7.5 mg at bedtime (sedative dose)</td>
<td>CNS depression</td>
<td>Can have interactions with sedating medications</td>
<td>Indications: circadian rhythm disturbance; jet lag; sleep-wake disturbance (inability to fall asleep)</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.125 mg at bedtime</td>
<td>Increased risk of bleeding; Lower seizure threshold; Anticholinergic effect</td>
<td>Sedation</td>
<td>Lower seizure threshold; Hypotension; Pruritus; Abnormal dreams; Black Box warning: suicide; Gabapentin; Trazodone</td>
</tr>
</tbody>
</table>

Source: Lexicomp

Sleep Medications

- Most without FDA approval for sleep or for children

<table>
<thead>
<tr>
<th>Class</th>
<th>Dosing Considerations</th>
<th>Potential Side Effects</th>
<th>Adverse Reactions</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trazodone</td>
<td>Antidepressant, antihistamine-antagonist 18 months-3 years: 25 mg at bedtime, increase by 25 mg to a max dose of 150 mg 3-5 years: 50 mg at bedtime, incremental increase to 150 mg 5+ years and Adolescents: Initial: 0.75 mg to 1 mg (up to a dose of 20 to 50 mg at bedtime, do not exceed adult dosing: 200 mg/day)</td>
<td>Increased risk of bleeding; Lower seizure threshold; Anticholinergic effect; Serotonin syndrome; Serotonin syndrome: Sertaline/prasertan; Pruritus; Abnormal dreams; Black Box warning: suicide</td>
<td>Some limited data in children with psychiatric disorders specifically focused on sleep</td>
<td>Indications: depressive, bipolar, panic disorders; Gabapentin; Trazodone</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.125 mg at bedtime (can increase to 0.25, 0.5, 0.75 mg after 2-3 week trial at each dose)</td>
<td>CNS depression</td>
<td>Sedation</td>
<td>CNS depression; Trazodone; Gabapentin; Trazodone</td>
</tr>
</tbody>
</table>

Source: Lexicomp
Some Sleep Medications to Consider

**First Tier**
1. Melatonin
2. Clonidine

**Clonazepam**
- Avoid in kids with intrauterine drug exposure
- Helpful for anxiety associated sleep onset insomnia
- Concomitant PLMs

**Trazodone**

**What about Diphenhydramine?**
- Children sometimes have paradoxical hyperactivity and lack of sleep when given diphenhydramine
- Often due to incorrect timing of administration
- Circadian surge of alertness or “second wind” occurs in evening
  - If medication given at that time, children become disinhibited and hyper, remain awake
- Tolerance is very common
- Long term cognitive issues (increased risk of dementia)

**Conclusion**
- Determining sleep issues in children with CHARGE can be challenging
  - Sleep history is essential
  - Educate and emphasize importance of sleep hygiene
  - Chronobiology
  - Evaluate and treat any condition that is “treatable”
  - Utility of sleep study
    - OSA
    - PLMs
  - Consider sleep medication
    - Trial and error
    - Choice of medication in line with other symptoms (PLMs, parasomnias, pain)

**References**


**Questions:**
- Susan.Wiley@cchmc.org
- Christine.Heubi@cchmc.org