Sleep in Children with CHARGE Syndrome

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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 a 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 in Children with CHARGE syndrome

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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

* Hartshorne T, Heussler H, Dailor AN, Williams GL, Papadopoulos D, Brandt K. Sleep disturbances in CHARGE syndrome: types and relationships with behavior and caregiver well-being Developmental Medicine & Child Neurology 2009, 51: 143–150.

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

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

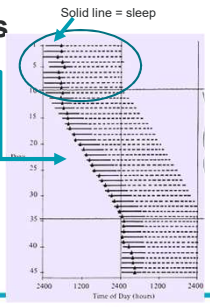
Chronobiology

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

http://yoursleep.aasmnet.org/pdf/sleepdiary.pdf

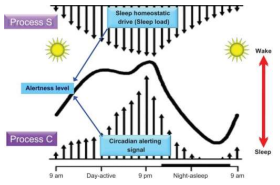
Circadian rhythm disorders

- 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 case, light boxes are helpful
    - Discontinue device and TV at least 1 hour before bedtime (blue light)
    - Keep electronics out of bedroom

Hull JT, Czeisler CA, Lockley SW. Suppression of melatonin secretion in totally visually blind people by ocular exposure to white light. Ophthalmology. 2018 Epub ahead of print.

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-decannulation
  - PSG
    - For capping study, downsize to 2.5/3.0
- Management of persistent OSA
  - CPAP should be considered
  - CineMRI and/or DISE (Drug Induced Sleep Endoscopy)

TABLE 2 Symptoms and Signs of OSAS

History
- Frequent snoring (≥3 nights/wk)
- Labored breathing during sleep
- Gasps/snorting noises/observed episodes of apnea
- Sleep enuresis (especially secondary enuresis)*
- Sleeping in a seated position or with the neck hyperextended
- Cyanosis
- Headaches on awakening
- Daytime sleepiness
- Attention deficit/hyperactivity disorder
- Learning problems

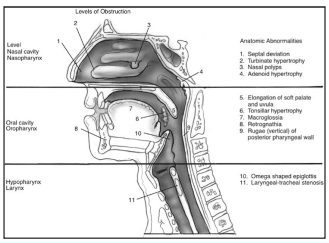
Physical examination
- Underweight or overweight
- Tonsillar hypertrophy
- Adenoidal facies
- Micrognathia/retrognathia
- High arched palate
- Failure to thrive
- Hypertension

* Enuresis after at least 6 mo of continence.

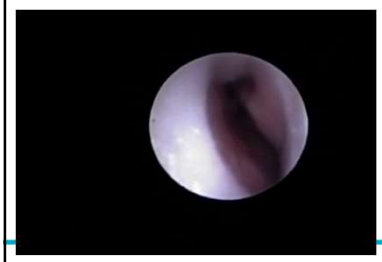
Marcus CL, Brooks LJ, Draper KA et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 2012;130:576-84.

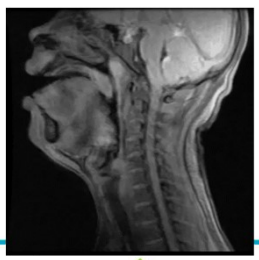
Evaluation for site of obstruction

- 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

Medication	*N*
Stimulants	8 (6 on one stimulant, 2 on two)
Dextroamphetamine	3
Methylphenidate	4
Atomoxetine	2
"ADHD meds"	1
Antipsychotics	11 (11 on one, 1 on two)
Aripiprazole	3
Haloperidol	1
Risperidone	6
Quetiapine	1
Olanzapine	1
Anxiolytics	3
Lorazepam	1
Clonazepam	1
Alprazolam	1
Antidepressants	21 (20 on one, 1 on two)
Clomipramine	2
Citalopram	3
Amitriptyline	1
Escitalopram	2
Fluvoxamine	4
Paroxetine	2
Fluoxetine	5
Bupropion	1
Sertraline	2
Mood stabilizers	6 (3 on one, 3 on two)
Valproic acid	4
Felbamate	1
Levetiracetam	1
Gabapentin	1
Topiramate	2
Antinarcoleptics	1
Modafinil	1
Antihypertensives	12
Clonidine	11
Propanolol	1

Wachel LE, Hartshorne TS, Dailor AN. Psychiatric Diagnoses and Psychotropic Medications in CHARGE Syndrome: A Pediatric Survey J Dev Phys Disabil (2007) 19:471–483.

Sleep Medications

Most without FDA approval for sleep or for children

	Class	Dosing considerations	Potential Side Effects, Adverse Reactions	Other considerations
Melatonin	Hormone	1 mg at dinner (low dose to prime the internal production) 2.5-10 mg at bedtime (sedative dose)	CNS depression Can have interactions with medications (increased sedation with benzodiazepines for example)	Indications: circadian rhythm disturbance, jet lag, sleep problems in individuals with vision impairment Pill, liquid, long-acting
Clonidine	Alpha Agonist	< 45 kg 0.1 mg, ½ tablet >45 kg, 0.1 mg at bedtime increase up to 0.3 mg Requires wean if not effective or planning to change to new medication	Low blood pressure, pulse CNS depression Arrhythmia Cardiology clearance if CHD	Off label indication for ADHD Pills, long-acting formulation, can be compounded into liquid

Source: Lexicomp

Sleep Medications

Most without FDA approval for sleep or for children

	Class	Dosing considerations	Potential Side Effects, Adverse Reactions	Other considerations
Mirtazapine	Anti-depressant	7.5-30 mg (45) Higher dose is not always more effective	Akathisia (activation, restlessness) Anticholinergic effects Arrhythmias Blood dyscrasias Serotonin syndrome Hyponatremia Lowered seizure threshold Black Box warning: suicide Stevens Johnson reaction	Comes in a solutab Typical indications for adults do not include sleep Can have anti-depressant withdrawal symptoms

Source: Lexicomp

Sleep Medications

Most without FDA approval for sleep or for children

	Class	Dosing Considerations	Side effects	Other considerations
Trazodone	Anti depressant, serotonin reuptake inhibitor/antagonist	**18 months-<3 years**: 25 mg at bedtime, increase by 25 mg to max dosage of 100 mg **3-5 years**: 50 mg at bedtime, incremental increase to 150 mg **>5 years and Adolescents**: Initial: 0.75 to 1 mg/kg/dose or 25 to 50 mg at bedtime; do not to exceed adult dosing: 200 mg/day)	Increased risk of bleeding Lower seizure threshold Arrhythmias Fractures Serotonin syndrome SIADH/hyponatremia Priapism Abnormal dreams Black Box warning: suicide	Some limited data in children with psychiatric disorders specifically focused on sleep When used for sleep, considered off-label use (in adults as well) Tablets only

Source: Lexicomp

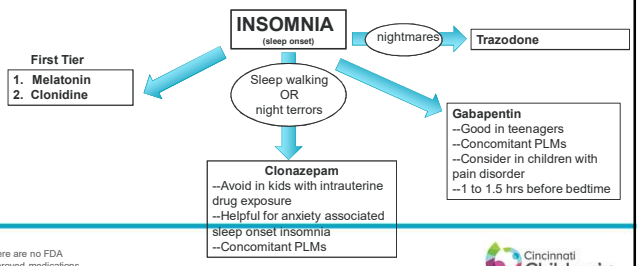
Sleep Medications

Most without FDA approval for sleep or for children

	Class	Dosing considerations	Potential Side Effects, Adverse Reactions	Other considerations
Clonazepam	Benzodiazepine	0.125 mg at bedtime (can increase to 0.25, 0.5, 0.75 mg after 2-3 week trial at each dose)	Ataxia, falls Paradoxical reaction (aggression) Respiratory depression Drug interactions (opioids, EtOH) Tolerance, abuse potential Undesired sleep behaviors Rebound insomnia **not typically seen at low dose	Indications: parasomnias, sleep onset insomnia, anxiety at sleep onset, PLMs Tablet, oral dissolving tab
Gabapentin	Anticonvulsant	Start 100 mg and titrate up to 900 mg if needed (1.5 hr before bedtime)	CNS depression Dizziness Drug interactions	Neuropathic pain PLMs Capsules, tablets, oral soln

Source: Lexicomp

Some Sleep Medications to Consider



There are no FDA approved medications for insomnia in children.

Sleep Medications

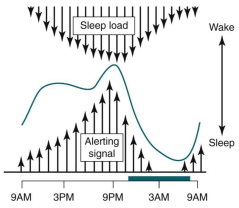
Most without FDA approval for sleep or for children

	Class	Dosing considerations	Potential Side Effects, Adverse Reactions	Other considerations
Suvorexant	Orexin receptor antagonist	5 mg (can go up to 20 mg) 30 min before bedtime	CNS depression Sleep related activities REM sleep effects Abuse potential Drug interactions	Indications: insomnia in adults ***Need to have failed most other meds first Pill (cannot crush)
Zolpidem	Non-benzo, benzo receptor agonist	5mg, 10 mg (start 2.5) CR (6.25, 12.5 mg)	CNS depression Abnormal thinking/behavioral changes Abuse potential Sleep related activities (Black Box Warning)—screen for parasomnias	Pills, long-acting formulation, can be compounded into liquid

Source: Lexicomp

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)



Insomnia. In: Berry R, ed. *Fundamentals of Sleep Medicine. 2012.*

Medications with common side effect of impacting sleep

Promotes wakefulness	Promotes sleep/somnolence
Albuterol nebs	Alpha agonists
Stimulants	Anticonvulsants
Diphenhydramine*	Psychotropic medications
Beta blockers	

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

- Hartshorne T, Heussler H, Dailor AN, Williams GL, Papadopoulos D, Brandt K. Sleep disturbances in CHARGE syndrome: types and relationships with behavior and caregiver well-being Developmental Medicine & Child *Neurology* 2009, 51: 143–150.
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Questions:
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