Update on sleep disorders in children

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Objectives

• At the end of this session, the participant would be able to
• Discuss poor sleep and its liabilities to parents and patients with supporting data from clinical research
• Discuss and provide options for diagnosis and treatment to parents and patients that will improve the outcome of the pediatric sleep disorder
Pre-test

• CASE: Steven is a 15 year old male
• pulmonary evaluation prior to enrollment in the Bariatric Surgery program
• morbidly obese, 165.3 kg, body mass index (BMI) of 52 (99th percentile)
• mild persistent asthma, allergic rhinitis – well controlled; FEV1 90% predicted
• obstructive sleep apnea (OSA) suspected
  • snoring, gasping for air, restless sleep, difficulty waking up in the morning and he has been missing early class periods in school
• tonsils were +3 in size bilaterally
• nasal congestion and boggy turbinates
• initial polysomnography showed severe obstructive sleep apnea with an AHI of 60 per hour.
Which of the following statements is true regarding Steven?

A. Immediate implementation of CPAP would be preferable for Steven

B. His OSA may augment the underlying low grade systemic inflammation that have been activated by his obesity

C. Significant morbidity is more neurocognitive and behavioral for Steven's age, whereas cardiovascular and metabolic will develop later into adulthood.

D. Steven has decreased risk for persistent OSA after adenotonsillectomy compared to a younger child.
Which of the following is true of pediatric sleep disorders?

A. Sleep fragmentation is related to neurohormonal changes but not to inflammation.

B. Parents should not be concerned with their child sleeping too little or too much because there is individual variability in sleep.

C. Phenotypic variability of pediatric OSA is related strongly to anatomical factors.

D. Pediatric sleep disorders have been linked to developmental delay, speech impairment and need for special education.
Reading list 2018

Wish we all could have a good night sleep!

• Rechtschaffen (1971) “if sleep does not serve an absolute vital function, then it is the biggest mistake the evolutionary process ever made…”

• Neuroplasticity
  - sleep linked to memory and learning
  - pediatric sleep disorders in the first 5 years of life associated with special educational need at 8 years of age

*Pediatrics* 2012;130:634–642
Recommended hours of sleep in children

- Ages 4-12 months: 12-16 hours (including naps)
- Ages 1-2 years: 11-14 hours (including naps)
- Ages 3-5 years: 10-13 hours (including naps)
- Age 6-12 years: 9-12 hours
- Age 13-18 years: 8-10 hours

- a consensus statement of the American Academy of Sleep Medicine
- endorsed by the American Academy of Pediatrics
- Sleep is essential for optimal health

Adverse consequences not just to immediate but to long-term health (adulthood)

- Pulmonary hypertension
- Cor pulmonale
- Endothelial dysfunction
- Insulin resistance
- Dyspilidemia
- Nocturnal enuresis
- Increased healthcare utilization
- Neurocognitive impairment
- Hyperactivity
- Attention deficits
- Concentration difficulties
- Impulsivity
- Excessive daytime sleepiness
Mechanisms of OSA

- upper airway narrowing
  - adenotonsillar hypertrophy
  - obesity

- upper airway collapsibility
  - decrease in muscle tone: neuromuscular diseases/cerebral palsy
  - airway inflammation: rhinitis
  - obesity

Airway patency
Starling resistor model

- when pressure outside the collapsible segment is greater than within the segment

- Children with OSA have significantly more collapsible UA with elevated $P_{crit}$ (less negative) during sleep
Assessment of airway collapsibility

• Complicated to perform – application of negative nasal pressure to sleeping patient
• Or needs equipment: acoustic pharyngometry
Surrogate markers for airway collapsibility

- inspiratory airflow limitation (pressure transducer)
- No difference in non-REM
- but in REM, OSA children with higher % inspiratory flow limitation (decreased compensatory neuromuscular response to upper airway obstruction)
- improved after adenotonsillectomy


flat inspiratory flow contour and increased inspiratory time relative to total respiratory time
Sleep endoscopy

• Should it be routinely performed prior to adenotonsillectomy? (so multilevel obstruction be identified)

• N=37
  - 33 with upper airway obstruction
  - 28 adenotonsillectomy,
  - 3 adenoidectomy, 2 tonsillectomy (91% success rate)
  - 4 non-surgical (CPAP/orthodontics)

• Controversial – routine (implications on resources and workloads)

• Mainly used for assessment of:
  • Residual OSA, post-AT, complicated OSA (e.g. craniofacial abnormalities, cerebral palsy, Down’s)


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5743164/
Brodsky tonsillar grading scale

Grade 1: tonsil occupies ≤25% of the oropharyngeal width to midline

Grade 2: Tonsil occupies 26%–50%

Grade 3: Tonsil occupies 51%–75%

Grade 4: Tonsil occupies >75%
Spectrum of pediatric obstructive sleep disordered breathing

• Primary snoring
  • habitual snoring for more than 3 nights per week without apneas, hypopneas, frequent arousals or gas exchange abnormalities (prevalence 7.45%)

• Upper airway resistance syndrome (UARS)
  • snoring, increased work of breathing and frequent arousals, without recognizable obstructive events or gas exchange abnormalities

• Obstructive hypoventilation
  • snoring plus elevated end-expiratory carbon dioxide partial pressure in the absence of recognizable obstructive events

• OSA syndrome
  • recurrent events of partial or complete upper airway obstruction (hypopneas, obstructive or mixed apneas) with disruption of normal oxygenation, ventilation and sleep pattern (prevalence 1% to 5%)
snoring with flow limitation on the nasal pressure airflow transducer – consistent with upper airway resistance
Obstructive hypopneas - snoring followed by reduced flow; presence of breathing effort but paradoxical; desaturations with recovery at the end of hypopnea.
Obstructive apneas - snoring and increase work of breathing followed by cessation of airflow; paradoxical breathing respiratory effort; desaturations and recovery at the end of each apnea.
Proposed classification of pediatric OSA

• two types of OSA in children (Gozal, et al)
  • Type I – adenotonsillar hypertrophy
  • Type II – obese children and adolescents
  • analogy with type I and type II diabetes

• (Type III - variety of craniofacial and neuromuscular disorders)
  • Crouzon and Apert syndromes, Pierre Robin sequence, Down syndrome, Goldenhar syndrome, achondroplasia, myelomeningocele, and cerebral palsy

Anatomical features → upper airway narrowing

• Micrognathia
• Macroglossia
• Midface hypoplasia

Treacher Collins syndrome, Crouzon syndrome, Apert syndrome, Pierre Robin sequence, achondroplasia, trisomy 21, Beckwith Wiedemann syndrome, mucopolysaccharidoses
Epidemic of obesity

• About 50% of overweight/obese children have obstructive sleep apnea (OSA) compared to up to 6% of normal weight children
  - Sleep 2014; 37:943-9

• every 1 kg/m2 increase in body mass index (BMI) above the mean for age and sex increases the risk of developing OSA by 12%
Obesity contributing to OSA in mechanical ways

• Fatty infiltrates within the upper airway (UA) structure and neck → UA narrowing → pharyngeal collapsibility
• Abdominal visceral fat limits diaphragmatic descent (especially when supine)
• Adipose tissue in chest wall - impair lung compliance → hypoventilation, atelectasis and VQ mismatch
Anatomical risk factors

- Younger – adenotonsillar hypertrophy + increased upper airway collapsibility

- Adolescents
  - Transitional period
  - Puberty – adipose alterations, hormonal changes
  - Similar to adult prototype?
    - Obese adolescents with OSA - more prominent daytime sleepiness symptoms
Anatomical risk profile for adolescents

• MRI scans of upper airway (n=137; 12-16 years) (Schwab, et al)

  • Obese adolescents with OSA; Obese controls; Lean controls
    - increased adenotonsillar size, small nasopharyngeal airway (increased soft tissue to craniofacial space ratio)
    - anatomical risk profile different from adult
    - gender differences larger tonsils for boys; larger adenoids for girls

  - Implications on adolescent OSA management strategy: surgical removal (or pharmacotherapy) before CPAP implementation

Liabilities of poor sleep in children

• cardiovascular
• metabolic
• neurobehavioral
• impaired cognitive function
Two key issues that underpin the development of OSA-related morbidities

- low grade systemic inflammation
- increased oxidative stress
OSA and inflammation evidences

• Nasal nitric oxide elevated in OSA and primary snoring (marker of airway inflammation)

• H2O2 in morning exhaled breath condensate elevated (marker of oxidative stress)

• pro-inflammatory cytokines, TNF-α, IL-6, and IL-8 elevated in serum
  • regulatory cytokines, IL-10 decreased
Neurocognitive and behavioral morbidities

• Probable mechanistic role?
• MRI data showed greater activity in regions of the brain implicated in cognitive control, conflict monitoring and attentional allocation for children with OSA (in order to perform same tasks at same level)

Behavioral and ADHD

- Overlap of symptoms

- even **mild OSA and habitual snoring** have been associated with hyperactivity, difficulties concentrating, attention problems and impulsivity

- Tucson Children’s Assessment of Sleep Apnea (TuCASA) study – children with untreated OSA had attention problems and hyperactivity, aggressive behaviours, lower social competencies, poor communication and/or diminished adaptive skills

- *Sleep 2013;36:517-525B.*
Sleep-disordered breathing and school performance in children (Gozal)

• a prospective study in first-grade school children

• OSA disproportionally high in the lowest 10% of their class

• while children treated for OSA showed significant academic improvement versus children who did not receive treatment did not improve

Childhood Adenotonsillectomy (CHAT) Study

• the first ever randomized controlled trial to compare adenotonsillectomy with watchful waiting

• primary outcome: change in the attention and executive-function score (Developmental Neuropsychological Assessment)

• adenotonsillectomy resulted in significant improvements in quality of life measures

• however, due to ethical considerations, recruited only mild OSA with no significant oxygen desaturations, above 4 years of age, only followed up for 7 months

• generalizations to other ages and severities of OSA are not possible

Chat study – comparison of sleep study and symptoms

- did not undergo adenotonsillectomy
  - 42% had resolution of OSA on follow-up PSG 7 months later (lower apnea-hypopnea index and waist circumference <90% percentile)
  - Only 15% experienced symptomatic resolution (lower sleep questionnaire and snoring scores)

Cardiovascular morbidities

oxidative stress alters the endothelial cells and leads to endothelial "dysfunction"

Genetic ↔ environment

Resolution after adenotonsillectomy but persist in subgroup with strong family history of cardiovascular disease

Severity is greater in children who are obese and have OSA
Metabolic morbidities

OSA in adults – well recognized
In children – discrepant findings

Post-pubertal adolescents – strong association between OSA and metabolic syndrome

Pre-pubertal children – lipid and cholesterol alterations and insulin resistance only seen with concurrent obesity

Phenotypic variations

• Spectrum of OSA is complex

Habitual snoring → upper airway resistance → hypoventilation → OSAS

• Difficulties
  
  AHI <1/hr TST on PSG, snore habitually with evidence of enuresis, neurocognitive, behavioral consequences  
  Versus significant AHI with no evidence of sequelae

Translational and personalized approaches for pediatric obstructive sleep apnea: ‘Omics’

- why at any level of disease severity, there are children who exhibit morbidity, and those who do not?

- environmental factors: smoking, pollution, diet and levels of physical activity

- genetic factors
  - examples: apolipoprotein E function to explain discrepancies in cognitive function; CRP and IL-6 gene variants in childhood OSA

- epigenetics: occur in OSA and may modify specific aspects of OSA-associated morbidity
  - example: children with high CRP levels exhibited increased methylation of the FOXP3 gene (linear correlation between FOXP3 DNA methylation levels and inflammatory markers)

Sleep fragmentation

• results in altered pro inflammatory pathways and higher levels of plasma adipokines
• associated with neurohormonal changes
• A key determinant in the development of neurocognitive dysfunction associated with OSAS may be the magnitude of this inflammatory response

Cognitive function and CRP

Sample of 278 children

Snoring

Non-snoring

Non-OSA

OSA

≥ 2 abnormal cognitive subtests

Mean hsCRP = 0.48+/−0.12 mg/dl

Mean hsCRP = 0.36+/−0.11 mg/dl (p<0.01)

Normal cognitive scores

Mean hsCRP = 0.21+/−0.08 mg/dl (p<0.002)

High-sensitivity C-reactive protein (hsCRP) levels higher in children with OSA, who particularly neurocognitive deficits

Mean hsCRP = 0.19+/−0.07 mg/dl

Mean hsCRP = 0.36+/−0.11 mg/dl (p<0.01)

Mean hsCRP = 0.48+/−0.12 mg/dl

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Adenotonsillectomy

• Outcome or success rate of adenotonsillectomy
  - true percentage? success rate: 75%-80% ???
  - recent study (multicenter retrospective): 30%
    - based on post-op PSG (AHI)

• Complications of T and A (meta-analysis)
  • Children with OSA appear to have more respiratory complications
  • Most frequent early complications are respiratory compromise and secondary hemorrhage

Medical management (pharmacotherapy)

- Tonsillar cultures in OSA: CD3, CD4 and CD8 lymphocytes and proinflammatory cytokines TNFα, IL-1α and IL-6 are increased.
- In vitro experiments: Corticosteroids were added to OSA tonsillar cell cultures, decreased proliferative rates and increased apoptosis, and reduction in the secretion of IL-6, IL-8 and TNFα.
- Randomized crossover trial of intranasal budesonide for mild OSA (6 weeks of therapy):
  - Reduction in OSA severity, decreased adenoidal size.

Leukotriene antagonists (LT)

• In vitro:
  • increased levels of leukotriene receptors 1 and 2 in tonsils from OSA
  • LT antagonists to tonsillar cell cultures with dose-dependent reductions in cellular proliferation and secretion of the cytokines TNFα, IL-6, and IL-12

• Clinically:
  • recent double-blind placebo-controlled study
    • Improvement in sleep disturbances

*Pediatrics* 2012;130: e575–80.
Risk factors for persistent OSA

- Obesity
- Severe OSA (AHI)>20/hr TST
- older age (>7 years)
- Asthma
- African ethnicity
- history of prematurity

Prematurity

• often associated with generalized muscle hypotonia
• atypical breathing pattern is associated with the development of mouth breathing and a high and narrow hard palate
• early premature infants often have abnormalities with feeding functions, such as suction, mastication, and swallowing
• weakness of orofacial muscles negatively alter craniofacial growth and lead to a small UA
CPAP in children

• Indications:
  • minimally enlarged tonsils and adenoids
  • residual OSA after adenotonsillectomy
• effective CPAP treatment linked with improvements in cognitive performance
• Adherence can be extremely challenging in children

Rapid maxillary expansion

- orthodontic appliance deliver a lateral force to the upper posterior molars, opens the midpalatal suture transversely and therefore widens the nasal cavity
Efficacy of RME (rapid maxillary expansion)

• may be a useful in children with malocclusion and OSA
• Goal: correct crossbite and to widen the maxilla and maxillary dental arch to reduce maxillary constriction (mouthbreathing)
  • help solve nasal airway and naso-respiratory problems
• 24 month follow up
  • 14 patients, PSGs at baseline, one year and 2 year
  • Only 2 out of 10 with treatment failure (tonsil hypertrophy and weight gain)

Urinary markers

• morning urinary samples
  - OSA may result in alterations in renal glomerular or tubular permeability (increased catabolism of proteins)
• nocturnal alterations in urinary neurotransmitters
  - episodic hypoxemia and arousals likely result in heightened sympathetic activity, and may be associated with increased levels of urinary catecholamines (epinephrine and norepinephrine)

Genomic and proteomic approaches in diagnosis and personalized treatment of OSA

Pipeline of approaches in diagnosis and personalized treatment of OSA

Summary

• Pathophysiology of OSA – mechanics of upper airway narrowing and increased airway collapsibility

• Yet, pediatric OSA spectrum is complex

• Phenotypic variations due to interplay of genetic, environmental, disease severity and individual susceptibility factors

• Is it time to look into personalized treatments for pediatric OSA - precision medicine, for improved outcomes?
Post-test

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Special populations
Down’s syndrome

- Poor sleep
  - reduced REM sleep and increased slow-wave sleep independent of OSA
- implications for learning, memory, and behavior
- Anatomy: maxillary hypoplasia and small nose with low nasal bridge midface
- Recurrent upper airway infections → adenotonsillar hypertrophy
- Hypotonia

Craniofacial anomalies

• clinical findings - snoring, work of breathing, desaturations
• congenital craniofacial anomalies is strongly associated with inpatient diagnosis of OSA
• anatomic features - maxillary or mandibular hypoplasia, crowded oropharynx, macroglossia, or poor motor tone

Craniosynostosis

- significant maxillary hypoplasia
- estimated prevalence of OSA of 53% in this population based on symptom report

Apert syndrome  Crouzon syndrome  Pfeiffer syndrome
Oromaxillofacial procedures

• surgical advancement of the midface to enlarge the upper airway
  Le Fort II or Le Fort III procedure (internal or external distraction devices)
• substantially reduced the AHI and improved oxygen saturation in a cohort of 11 children (Pfeiffer, Cruzon, or Apert syndrome and severe OSAS)
• external transfacial pin for distraction

Pierre Robin Sequence
Treatment strategies depend on the severity of compromised airways

- palatal plate with a pharyngeal extension
- Palatal obturator with dorsal extension
- Nasopharyngeal intubation
- Glossopexy
- Mandibular distraction osteogenesis
- Tracheotomy
- Timely and sequential palatal reconstruction

Suction and drinking plate with pharyngeal extension
Pierre Robin sequence surgery

- Tongue-lip adhesion and tongue repositioning can improve apnea/hypopnea index (AHI) and oxygenation saturations
- Systematic review (90 patients)
  - Tongue-lip adhesion
    - AHI from 30 to 18 events per hour (50% reduction)
    - Lowest oxygen saturation from 75% to 84%
  - Tongue repositioning
    - AHI from 46 to 17 events per hour (62% reduction)
    - Mean oxygen saturation from 90 to 95%

Autism spectrum disorder (ASD)

• Sleep problems as high as 80% in children with ASD
• Sleep problems and insufficient sleep →
  - daytime sleepiness, learning problems and behavioral issues
  - hyperactivity, inattentiveness and aggression
• most common sleep problems
  - difficulty falling asleep and repeated awakenings
  - very prolonged awakenings or awaken very early for the day
  - sleep of other family members is often impacted
Poor sleep in ASD

• Neurological
  - abnormalities in brain systems that regulate sleep
  - melatonin and other chemicals released by the brain
• Medical
  - epilepsy or gastroesophageal reflux can disrupt sleep
  - medications taken can be alerting and contribute to difficulty falling asleep
• Psychiatric
  - anxiety and/or depression can interfere with sleep
• Behavioral
  - poor sleep hygiene and limit-setting problems
• Others: sleep apnea, sleepwalking, nightmares, restless legs syndrome