Conflict of Interest Disclosure

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I have no financial relationships with a commercial entity producing healthcare-related products and/or services.
From ZZZ's to F's: Obstructive Sleep Apnea as a Major Cause of Cognitive and Behavioral Impairment in Children

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OSA: epidemiology
- Infants: 1-2%
- Children ages 2-18: 2-3-5%
- Prepubertal ♂=♀
- Adults
  - Women 2-4%
  - Men 3-7%

Two peaks of incidence
- Between the ages of 3-6
- In adolescence concurrent to rise in obesity

Upper airway obstruction during sleep: a spectrum
- Normal breathing
- Primary snoring
- Upper airway resistance syndrome
- Obstructive hypoventilation
- OSA

Definitions
- Hypopnea: reduction of airflow by ≥50% for 2 breath cycles with ≥3% change in SaO₂ and/or arousal
- Apnea: reduction of airflow by ≥90% lasting for 2 breath cycles
- Apnea hypopnea index (AHI): number of apneas+hypopneas/hour

Sequence of events in normal breathing
- Signal sent from respiratory center in brain to respiratory muscles
- Diaphragmatic contraction
- Abdominal, thoracic excursion
- Negative intrathoracic pressure generation
- Air entry into lungs
- Gas exchange
- Exhalation

Katz and Marcus. Diagnosis of obstructive sleep apnea syndrome in infants and children.
Sheldon et al. Principles and Practice of Pediatric Sleep Medicine, Saunders 2005.
With decreased upper airway diameter:

- Increase in negative pressure gradient across the “choke point” in the upper airway
- Increased negative pressure forces on lumen
- Partial/completion upper airway obstruction
  - Changes in SaO2, ETCO2
- Autonomic activation (sympathetic surge)
- Termination of event via arousal (EEG, physical)

OSA: the sum of many variables

- Reduced muscle tone:
  - Sleep stage (REM/NREM)
  - Central/trunk hypotonia
  - Medications
- Body position
- Anatomic:
  - Craniofacial
  - Macroglossia
  - Laryngomalacia

Anatomic (continued):

- Hypertrophy of the adenoids, tonsils
- Fat deposition

Inflammation of soft tissues:

- GERD
- Environmental tobacco smoke
- Allergies
- Upper respiratory tract infections

OSA in children

- Adenotonsillar hypertrophy, obesity most common precipitating causes
- Superior UAW site of obstruction in most cases (area of adenoid and soft palate)

The adenoids
Adenoidal hypertrophy

Consequences of OSA: general
- Excessive daytime sleepiness
- Hypertension
- Impaired glucose tolerance
- Metabolic syndrome
- Increased cardio/cerebrovascular disease
- Pulmonary hypertension
- Right sided heart failure

Specific to children
- Failure to thrive
- Developmental delay
- Executive function impairment
- Cognitive impairment
  - Memory
  - Intelligence
- Decreased school performance
- Attention Deficit and Hyperactivity (ADHD)

Excessive daytime sleepiness
- Present in 7% of children with OSA per parental report (Carrol, McColey et al. Chest 1995)
- Present in 43% of children scheduled for T&A by PSQ-SS (Chervin, Weatherly et al. Sleep 2006)

Snore Associated Sleep Fragmentation in Infancy: Mental Development Effects and Contribution of Secondhand Cigarette Smoke Exposure
Montgomery-Downs and Gozal, Pediatrics 2006
35 healthy community infants age 7.2-9.5 months old:
- Underwent overnight sleep study
- Tested with Bayley Scales of Infant Development, consisting of Mental Development Index (MDI) and motor assessment, on the morning after the sleep study

No scored apnea, hypopnea (only respiratory effort related arousals)
- Respiratory arousals correlated with reduced scores on MDI
- Infants from smoking household more likely to have increased respiratory arousals
- MDI did not differ between non/smoking households

Sleep Disordered Breathing, Behavior and Cognition In Children Before and After Adenotonsillectomy

Chervin, Ruzicka et al., Pediatrics 2006

105 children (age 5-12.9) referred to surgical outpatient clinics
- 78: T&A (71 with clinical diagnosis of OSA)
- 12: hernia repair
- 15: managed non-operatively
- All underwent sleep study, neuropsychiatric evaluation, parental behavioral rating
- Had repeat assessment one year later

Baseline AHI of T&A group = 7.3 ± 12.5
Baseline AHI of control group = 0.2 ± 0.4
40% of T&A, 4% controls with OSA
28% (22/78) of the T&A group had ADHD at baseline compared with 7% (2/27) of controls, difference disappeared one year later
Parental behavior rating of hyperactivity decreased by 0.5 SD

However...
The improvement in cognitive, behavioral measures amongst those children who underwent T&A did NOT correlate with presence/absence of OSA

Why not?
- Cortical arousals
- Sub-cortical arousals
- Autonomic arousals
Sleep disordered breathing and school performance in children
David Gozal, Pediatrics 1998

- 297 first graders in lowest 10th percentile of their class
- All screened for sleep associated gas exchange abnormalities defined as:
  - TCCO₂ > 8 mmHg of waking values, > 60% of the night
  - SpO₂ reductions of > 5%, or drops < 90%
- 54 identified with abnormalities:
  - 24 underwent T&A
  - 30 untreated

Grades improved in those children treated with T&A, but NOT:
- In those who did not undergo surgery
- In those without sleep associated gas exchange abnormalities

Childhood Obstructive Sleep Apnea Associates With Neuropsychological Deficits and Neuronal Brain Injury
Halbower, Degaonkar et al., PLOS Med 2006

- 31 children ages 6-16 (19 OSA, 12 controls) cross matched for age, gender, SES
- Underwent sleep study, neuropsychiatric assessment, MR spectroscopy (measuring steady state levels of native metabolites in the brain)

- OSA:
  - AHI: 34.6 ± 31.5; AI 15.7 ± 16.7
- Controls:
  - AHI: 0.2 ± 0.3; AI 5 ± 2.2
Those children with OSA had deficits in:
- IQ
- Verbal working memory
- Verbal fluency

Children with OSA had:
- Decreases in N-acetyl aspartate/choline ratio in left hippocampus, right frontal cortex, representative of neuronal damage

Proposed etiologic mechanisms for the developmental, cognitive and behavioral deficits seen with OSA:
- Intermittent hypoxia
- Inflammation
- Changes in cerebral blood flow
- Disruption of neural repair mechanisms (apolipoprotein E)

Intermittent hypoxia during development induces long term alterations in spatial working memory, monoamines, and dendritic branching in rat frontal cortex

Keirandish, Gozal et al., Pediatr Res 2005

Rats exposed to room air (RA) or to intermittent hypoxia (IH) of 90 second alternating intervals of FiO₂ of 0.1/0.21 during the day (but not at night) for 14 days starting at post-natal day 10
- Water maze working memory test conducted at 4 months of age
- Male rats exposed to IH had working memory deficits, decreased dendritic branching in frontal cortex

Hypoxia and inflammation:
- Direct hypoxic injury
- Activation of inflammatory pathways by the intermittent hypoxia:
  - Intermittent hypoxia leading to oxidative stress (demonstrated in a rat model)
  - CRP levels correlate with reduced cognition in children with similar degrees of OSA
  - Obesity correlated with increased daytime sleepiness in children with similar degrees of OSA

Changes in cerebral blood flow:
- Increased middle cerebral artery blood flow:
  - Correlated with neuropsychological deficits in children with sickle cell disease
  - Normalizes in children with OSA s/p T&A, concurrent to improvement in executive function

In summary:

› OSA is under recognized and under treated
› Has neurocognitive, developmental and behavioural sequelae unique to children

Outstanding questions:

› What is (ab)normal?
› Is primary snoring pathological?
› How much obstruction is too much?
› When do the neurocognitive, developmental and behavioral changes become irreversible?