Pediatric Sleep-disordered Breathing: Pathophysiology and Consequences

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None

Pediatric OSA: Timeline

1976 Case Series
1981 CRAP
2011 Personalized Medicine

Personalized Medicine
• Medical care tailored to the clinical phenotype combined with the genomic & molecular profile, to better predict morbidity and Rx outcome
• Shift of emphasis towards screening, early/targeted Rx, and prevention

Pediatric OSA: Overview

Anatomy
Craniofacial size
Soft tissues
Fat distribution

Neuromuscular
Muscle recruitment
Arousal threshold
Ventilatory control
Lung Volume

OSA
Sleep
Intermittent Hypoxia
Sleep Fragmentation
Hypoventilation
↑ Respiratory Effort

Genet trait susceptibility
Environment

Consequences
Endocrine
Metabolic
Cardiovascular
Neurocognitive
Autonomic

Pediatric OSA: Epidemiology

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snoring</td>
<td>8 – 10%</td>
<td>50%</td>
</tr>
<tr>
<td>OSA</td>
<td>2 – 3%</td>
<td>30%</td>
</tr>
<tr>
<td>Overall</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

OSA
Visceral Fat
Subcutaneous Fat
Pediatric OSA: Epidemiology

- ↑ risk in African Americans
  - Redline et al, AJRCCM 1999: 159; 1527-
- ↑ in males, especially after puberty
  - Archbold et al, J Ped 2002; 140: 97-
- Associations: SES, neighborhood disadvantage, prematurity, asthma
  - Spilsbury et al, J Peds 2006: 149; 342-
- Age not important determinant of OSA in children

OSA: Children vs. Adults

<table>
<thead>
<tr>
<th></th>
<th>Children (Lean &amp; ATH)</th>
<th>Obese/Mild ATH</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleepiness</td>
<td>+</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Hyperactive</td>
<td>++++</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>+</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Metabolic</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>Depression</td>
<td>+</td>
<td>+</td>
<td>++++</td>
</tr>
</tbody>
</table>

Capdevila et al, Proc ATS 2008: 5; 274-

OSA: Children vs. Adults

- Apnea or Hypopnea
- Respiratory effort related arousals (RERA)
- Hypoventilation
- Desaturation
- ↑ Respiratory effort (sustained or crescendo)
- Tachypnea
- Flow limitation
- Autonomic arousals
- Snoring

Quilichini et al, Arch Pediatr Med 2004; 158:153-
Urschlitz et al, AJRCCM 2003; 168: 464-
Banden et al J Obst Ecol Neuro Psycho 2000; 22: 554-
O’Brien et al, Peds 2004; 114: 44-
Goodwin et al, SLEEP 2003; 26: 587-
Gotlib et al, J Peds 2004; 145; 430-

Obstructive Hypoventilation

Katz et al, Sleep Apnea, NHLBI, 2011 in press
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Sleep onset: OSA Patient

<table>
<thead>
<tr>
<th></th>
<th>Wake</th>
<th>Sleep</th>
<th>Sleep</th>
<th>Arousal</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG Raw</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG MTA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Katz et al, AJRCCM 2010; 168: 854

Sleep Apnea Phenotyping

Anatomy
- Craniofacial size
- Soft tissue structures
- Fat distribution

Neuromuscular
- Muscle recruitment
- Inspiratory duty cycle
- Arousal threshold
- Ventilatory control
- Lung Volume
- Vascular volume

Intermittent Hypoxia
- Sleep Fragmentation
- Alveolar Hypoventilation
- Respiratory Effort

Upper Airway Ontogeny

Arens et al, SLEEP 2004; 27: 997

Adenotonsillar Growth

Jeans et al, Br J Rad 1981; 54 117

Dentofacial ontogeny: Breathing route

Normal Palate

Dentofacial ontogeny: Breathing route

Normal
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Dentofacial ontogeny: Breathing route

Nose breathing

Mouth breathing

Palate

Teeth

High-arched Narrow maxilla

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Long Face Syndrome

Features
- Vertical height
- "gummy" smile
- High–arched palate
- Steep mandibular plane
- Disuse atrophy of nose

Etiology
- Nasal obstruction affects craniofacial morphology

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OSA: Anatomy

Normal

OSA

Donnelly et al, Radiol 2003, 227: 239-Y

ATH No OSA

OSA

Donnelly et al, Radiol 2003, 227: 239-Y

Donnelly et al, AJR 2002, 179: 105-

Recurrent OSA: Lingual tonsils

Normal

Enlarged lingual

Donnelly et al, Sem Ultra CT MRI 2010, 21: 107-

• Down’s syndrome (17%)
• Obesity
• Dx with MRI
• Other: glossopptosis, hypopharyngeal collapse

*Anatomy accounts for only 34% of the variance in OSA severity

Younes et al, AJRCCM 2003, 168: 845-
Causes of increased UA resistance

Sleep onset: OSA Patient

Airway Muscle (EMGgg): Apnea/hypopnea

Successful neuromuscular compensation

EMGgg & Flow: Response to negative pressure
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Arousal

- Transient intrusion of heightened vigilance
- Graded phenomenon (sub-cortical → EEG → Behavioral)
- Spontaneous or reactive

- Most arousable in REM
- Threshold increases with sleep debt
- Induced arousals associated with neurocognitive dysfn

Fuller et al, J Biol Rhyth 2006; 21: 482-
Katz et al, AJRCCM 2006; 173: 902-

Arousal: Autonomic

- Sympathetic activity
- Catecholamines
- Subtle sleep disruption

- EEG
- Pulse Transit Time
- Peripheral arterial tonometer

Obrien et al, J Clin Sleep Med 2007; 3; 41-

OSA: Clinical Classification

- Airway Collapsibility (Anatomy)
- Sleep-disordered breathing
- Snoring
- Stable
- Difficult

- Arousal Threshold
- Easily

OSA: Adverse Sequelae

- Airway Collapse
- Intermittent Hypoxia
- Sleep Fragmentation
- Alveolar Hypoventilation
- Respiratory Effort

- Endocrine
- Metabolic
- Cardiovascular
- Neurocognitive
- Autonomic

Pediatric OSA: Cardiovascular

- Systemic hypertension
  - Enright et al, Arch Ped Adolesc Med 2003; 157:901-
- Endothelial dysfunction
  - Gozal et al, Circ 2007; 116: 2307-
- Absent BP “dip” during sleep
  - Anfin et al, AJRCCM 2004; 169: 950-
- LV dysfunction
  - Anfin et al, AJRCCM 2002; 165:1395-
- Pulmonary hypertension
  - Duman et al, Int J Cardio Imaging 2008; 24: 261-
- Abnormal HRV
  - Aljadeff et al, SLEEP 1997; 20: 151-
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Pathophysiology and Consequences

OSA: Metabolic Consequences

- ↑TNF-α & CRP in OSA
  Gozal et al, SLEEP 2010; 33:319-
- Obese children with OSA & short sleep have ↑ MS
  de la Elva et al, J Peds 2002; 140:684-
  Flint et al, J Peds 2007; 150:364-
- Children with OSA have ↑ risk of liver steatosis
  Kheirandish-Gozal et al, Chest 2008; 133: 92-
- Leptin levels are ↑ in children OSA
  Tauman et al, SLEEP 2007; 30:443-
- Hyperlipidemia
  Gozal et al, AJRCCM 2008; 177:1142-

OSA: Neurobehavioral consequences

- Hyperactivity/Inattentive
  Chervin et al, 2002; 109:449-
- Poor school performance
  Gozal et al, Pediatrics 1998; 102: 616-
- Aggressive behavior
  Gottlieb et al, Pediatrics 2003; 112:870-
- Excessive daytime sleepiness uncommon with AHI <20/hr
  Gozal et al, Pediatrics 2001; 108: 693-
- Cognitive deficits co-vary with endothelial dysfunction
  Gozal et al, Pediatrics 2010; 126; e1161-

School performance

Adolescents who previously snored at 4-6 yo

![Graph showing school performance for adolescents who previously snored at 4-6 yo](image)

School performance

Adolescents who previously snored at 4-6 yo

![Graph showing school performance for adolescents who previously snored at 4-6 yo](image)

Does Benign "Primary Snoring" Ever Exist in Children?

The American Academy of Pediatrics has recommended that all children who snore be evaluated.

Considerable evidence that Snoring & AHI <1 event/hour is associated with neurocognitive impairment independent of apnea or hypoxemia

- Urschitz et al, AJRCCM 2003; 168: 464-
- Urschitz et al, Ped 2004; 114: 1041-
- Bumstein et al, J Clin Exp Neuropsychol 2000; 22: 554-
- O'Brien et al, Peds 2004, 114: 44-
- Gozal et al, SLEEP 2003; 26: 587-
- Gottlieb et al, J Peds 2004, 145: 435-
- Guilleminault et al, Arch Ped Adol Med 2004, 158:153-