The Role of Obesity and Inflammation in Pediatric Sleep-Disordered Breathing

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Objectives:

At the end of this session, the participant would be able to:

1. Explain the interaction of obesity and pediatric sleep disordered breathing in activating the inflammatory pathway

2. Identify the metabolic alterations and complications stemming from this shared inflammatory pathway
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.
Obstructive sleep apnea in children

• Incidence of 2–3% of all children
• peak prevalence between 2 and 8 years
Overweight/obese children and obstructive sleep apnea (OSA)

• up to 50% of overweight/obese children have obstructive sleep apnea (OSA) compared to up to 6% of normal weight children

• prevalence of childhood obesity has doubled in the last 30 years (between 1980 and 2010)
  • 6-11 years old
    - increased from 7% to 18%
  • 12-19 years
    - increased from 5% to 18%

JAMA 2012;307: 483e90
BMI and OSA severity

• in children, 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%
• the severity of OSA is increased in obese children compared to that in normal weight controls
Fight and flight

• an interruption of normal sleep architecture
• alterations in gas exchange
  • repetitive decreases in oxygen saturation followed by rapid re-oxygenation
  • episodic hypercapnia
• occlusion of the upper airway
  • large fluxes in intrathoracic pressure
  • recurrent brain arousals
• induces potent and sustained activation of sympathetic nervous system
What happens when your sympathetic nervous system is activated?
Stress hormones during sleep!!!
Figure 1 | Physiological functions of leptin and ghrelin. Leptin and ghrelin are...
Liabilities

- Neurocognitive and behavioral disturbances
  - delays in the treatment may lead to decline in cognitive function (reduced or failing academic performance - Gozal, 2001)

- Cardiovascular morbidity
  - Endothelial dysfunction (a marker of subclinical cardiovascular disease)
  - Systemic hypertension
  - Pulmonary hypertension
  - Myocardial left ventricular remodeling

Pediatrics 2001;107:1394–1399;
short-term and long-term implications of OSAS could be amplified by the concurrent presence of obesity
Sleep fragmentation

• associated with neurohormonal changes
• altered pro inflammatory pathways
• neurocognitive dysfunction associated with OSAS may be related to the magnitude of this inflammatory response
Cognitive function

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

• Recent study: 278 children, 5 to 7 years
  • Both snoring and non-snoring children
  • overnight polysomnography, neurocognitive testing and a blood draw the next morning

Cognitive function and CRP

Sample of 278 children

Snoring

Non-snoring

Non-OSA

OSA

≥ 2 abnormal cognitive subtests

Mean hsCRP = 0.19 +/- 0.07 mg/dl

Mean hsCRP = 0.48 +/- 0.12 mg/dl

Normal cognitive scores

Mean hsCRP = 0.36 +/- 0.11 mg/dl

Mean hsCRP = 0.21 +/- 0.08 mg/dl

(p < 0.01)

(p < 0.002)

High-sensitivity C-reactive protein (hsCRP) levels

Obesity and Obstructive sleep apnea syndrome (OSAS) share common chronic inflammatory pathways.
Fig. 1. Hypothetical interaction of obstructive sleep apnea syndrome and obesity in activating pathways leading to metabolic disease. TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; CRP, C-reactive protein.
Mechanisms of OSA

- Intrinsic upper airway narrowing
  - Adenotonsillar hypertrophy
  - Obesity

- Increased upper airway collapsibility
  - Neuromuscular diseases
  - Airway inflammation
  - Obesity

Airway patency
Pathophysiology of OSA

• In children: adenotonsillar hypertrophy
  • reduce anatomical patency of the airway
    → exponential increases in pharyngeal resistance
    → episodic airway collapse

• several other risk factors such as obesity, craniofacial and neuromuscular elements independently contribute to the risk of OSA
Interesting...

- Adenotonsillar tissues from OSA
  - inflammatory cell proliferation
  - pro-inflammatory cytokines and mediators (e.g., TNF-a, IL-6, and IL-1alpha)

- compared to adenotonsillar tissues removed in children with recurrent tonsillitis

Interesting...

- recurrent vibration in the upper airway
  - promote localized inflammation leads to overexpression of inflammatory cytokines (animal models)
- exhaled breath condensate and induced sputum in children with OSA
  - upregulation of localized inflammatory processes in upper airway
Emerging epidemic of obesity

• prevalence rates of 7% to 22% of children in Western countries

• each increase of 1 kg/m² of BMI above the mean in children, the risk of OSAS increases by 12%

• the severity of OSA is increased in obese children compared to that in normal weight controls

Phenotype of OSA in children is also changing

• With obesity epidemic, a phenotypic variant of OSA in children and adolescents
  • closely resembles OSA in adults

• two types of OSA in children
  • divided into types I and II pediatric OSA
    • Type I – adenotonsillar hypertrophy
    • Type II – obese children and adolescents
  • analogy with type I and type II diabetes
OSA and obesity studies

• the risk for residual OSAS is markedly greater in obese children

• children with persistent OSAS after 5 years are at an elevated risk of developing obesity

• the degree of adenotonsillar hypertrophy required is lesser in obese children

• Obesity-induced OSAS behaves differently from OSAS phenotype exclusively induced by adenotonsillar hypertrophy
Anatomical risk factors

• Younger – adenotonsillar hypertrophy + increased upper airway collapsibility

• Adolescents
  • Transitional period
  • Puberty – adipose alterations, hormonal changes
  • Similar to adult prototype?
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

Obesity in children

• a multisystemic disease
• elevated risk of psychological disturbances
  • depression, suicidality, poor peer relationships
• gastrointestinal complications (GERD, hepatic disease, irritable bowel syndrome)
• Metabolic syndrome or insulin-resistance syndrome (4% of adolescents) but the prevalence of 30–50% in overweight/obese children
Obesity (continued)

• significant increase in the prevalence of childhood type 2 diabetes mellitus
• subsequent increases in early onset cardiovascular disease and cardiovascular risk factors (hypertension, left ventricular hypertrophy, dyslipidemia, and atherosclerosis)
Blood pressure and heart rate in obese/overweight children with OSA

- being overweight/obese had both independent and additive effects on BP and HR in children with OSA

Sleep Medicine 41 (2018) 58e68
Childhood into adulthood

• Elevated BP during childhood is a predictor of elevated BP and hypertension in adulthood
• Obesity in adolescence is a risk factor for early development of type 2 diabetes, and atherosclerosis and metabolic syndrome
• Obese adolescents with OSA may be at increased risk of developing these chronic cardiovascular diseases

The connection

• Obstructive Sleep Apnea, Inflammation, and the Metabolic Syndrome

OSAS may favour development of the MetS...

...or be a manifestation of the MetS

...or hypoxia might be the link between OSAS and the MetS
Obesity as chronic state of low-grade systemic inflammation

National Health and Nutrition Examination Survey (NHANES)
BMI was the best predictor of elevated C-reactive protein (CRP)
The Metabolic Syndrome in Children and Adolescents
Lipid and metabolic profiles

- the effect of **OSAS treatment** on lipid and metabolic profiles
  - 62 children (37 obese and 25 non-obese) with sleep studies

- significant associations between OSA parameters and the following:
  - serum insulin/glucose ratios
  - low-density lipoprotein (LDL) levels
  - high-density lipoprotein (HDL) levels
  - LDL/HDL ratio
  - apolipoprotein B (ApoB)

Effect of treatment of OSA

- significant reductions of LDL and ApoB
- reciprocal increases in HDL in both obese and non-obese
- insulin sensitivity improved in obese children
- marked improvements in metabolic control
Leptin and ghrelin
Leptin and ghrelin

• Leptin
  • a mediator of long-term regulation of energy balance, suppressing food intake and thereby inducing weight loss

• Ghrelin
  • fast-acting hormone, role in meal initiation

• obese subjects
  • hormone leptin is increased - anorexigenic
  • hormone ghrelin is decreased - orexigenic
  • but established-obese patients are leptin-resistant
Sleep duration and weight gain

• Epidemic of obesity with parallel growth in chronic sleep deprivation
• Society: demands and diet
  • influence on leptin and ghrelin secretion and functioning
• potentials of leptin and ghrelin as drug targets

Systemic inflammation and leptin

- White adipose tissue produce over 50 molecules termed **adipokines** with various functions (specific inflammatory and metabolic regulation)

- **Leptin**, a cytokine
  - Regulation of body adiposity through promotion of satiety
  - Important immunomodulatory role
Leptin (continued)

• stimulates production of pro-inflammatory cytokines (IL-6 and TNF-alpha)
  • which are independently induced by OSAS
• typically elevated in obesity
• But leptin is the “bad guy”
  • systemic inflammation provoked by obesity is related to elevated circulating leptin
  • independent risk factor for cardiovascular disease
In adults

- OSAS leads to elevated circulating levels of leptin

- Effective resolution of OSAS will reduce leptin levels particularly in adults who are non-obese
In children

• 130 children with sleep studies:
  • Plasma adipokine concentrations
  • association between the degree of obesity and circulating leptin levels
  • accentuated in the presence of co-morbid OSAS
• increase in circulating leptin levels induced by OSAS remained significant even after adjusting for the degree of obesity

Relationships between OSA and obesity, insulin resistance, the metabolic syndrome, and cardiovascular disease.
TNF-α

• Tumor necrosis factor-α
• Pro-inflammatory cytokine
• Promotes expression of cellular adhesion molecules (leukocytes with the vascular endothelium)
• Stimulating atheromatous plaque formation
• Correlate with severity of daytime sleepiness and degree of hypoxia induced by OSAS
Sleep disordered breathing (SDB), inflammation, and Uric Acid

- effects of SDB on inflammation and oxidative stress in childhood obesity
- weight loss is an effective treatment in obese SDB cases
- Uric acid as a good reflector of oxidative stress, decreasing in concentration as SDB improved

*Obesity*, 2012. 20(1), 172-177.
Adenotonsillectomy in Obese Children

• study to analyze the effects of adenotonsillectomy (removal of adenoids and tonsils) on plasma-based inflammatory biomarkers

• significant decreases of biomarkers such as IL-6, IL-18, PAI-1, MCP-1

• evidence that interactive pro-inflammatory effects of sleep disorders contribute to downstream end-organ morbidities

Sleep disordered breathing (SDB) and C-reactive protein

• Elevated C-reactive protein (CRP)
  • risk factor for cardiovascular disease
  • independently correlated with obstructive sleep apnea syndrome (OSAS) in adults

Sleep And Breathing, 2014. 18(2), 335-340.
In children

• TNF-alpha

• Recent study:
  • Children with sleep studies
  • Morning plasma samples:
  • TNF-alpha levels significantly correlated with the degree of *respiratory-induced sleep fragmentation* (in children with OSAS)

• presence or absence of gene polymorphisms on the gene encoding for TNF-alpha

Sleep 2010;33:319–325.
Message

• great concern to all pediatricians
  • onset of cardiovascular disease in the context of obesity, OSAS, or both
  • develop at a very early stage of life (during childhood)
  • the true impact of such inflammatory and atherogenic alterations will only become apparent during adulthood

• The recognition and treatment of both obesity and OSAS is of paramount importance and urgency in children
Complexity of interactions...

- between obesity, OSAS, and activated inflammatory pathways
- recognition of additional potential interactions between environmental and lifestyle elements, and modulatory effects of gene polymorphisms
Have to be integrated...

• a single multifactorial model
• develop predictive and reliable algorithms
  • to identify the risks for short-term and long-term morbidity in children with obesity and OSAS
American Academy of Pediatrics

• Treatment of Metabolic syndrome involves both behavioral and pharmacotherapeutic interventions aimed at reducing obesity, glucose abnormalities, hypertension, and dyslipidemia.

• pediatricians should treat these component risk factors by using current best practices to reduce future risk for cardiometabolic disease
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shared inflammatory pathways with obesity and obstructive sleep apnea syndrome
References


References (2)


References (3)
