Is Sleep Apnea Affecting my Brain?: Cognitive Impairment in Obstructive Sleep Apnea Syndrome

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Learning Objectives

• Impact of obstructive sleep apnea syndrome (OSAS) on cognition
• Risk factors and pathophysiology of cognitive impairment (CI) in OSAS
• Future research opportunities........................!!!
Epidemiology

- Obstructive sleep apnea syndrome (OSAS) affects approximately 15 million adult Americans (1)
- OSAS is seen in a large proportion of patients who have hypertension, coronary artery disease, stroke and atrial fibrillation (2)
- Prevalence of OSAS is 2% in women and 4% in men in the 30-60 year age group (3)

(2) Lattimore JD et al, Obstructive sleep apnea and cardiovascular disease J Am Coll Cardiol 2003;41:1429-1437.
(3) Young T et al, The occurrence of sleep-disordered breathing among middle-aged adults, NEJM1993 Apr 29;328(17):1230-5
Definitions

• OSAS is characterized by repetitive interruption of ventilation during sleep caused by collapse of the pharyngeal airway

• **Apnea** is ≥ 90% decrease in airflow for > 10 seconds

• **Hypopnea (AASM definition)**: decrease in airflow to ≥ 30% for 10 seconds with ≥ 3% desaturation or arousal

• **Ongoing respiratory effort** characterizes obstructive events
Partial and complete airway obstruction resulting in hypopnea and apnea, respectively

Somers, V. K. et al. J Am Coll Cardiol 2008;52:686-717
Prevalence of CI in OSAS

• Cross-sectional study of 49 consecutive OSAS patients showed that 1 in 4 patients had CI \(^{(1)}\)

• APPLES (Apnea Positive Pressure Long term Efficacy Study), cross-sectional analyses of polysomnographic and neurocognitive data in 1204 adult OSAS patients at baseline \(^{(2)}\)

(1) Antonelli Incalzi R et al, *Journal of sleep research* 2004
(2) Quan SF et al, *Sleep* 2011
Case 1

• A 52 year old male patient with a history of recent ischemic stroke and OSAS presents to clinic for follow up

• Additional PMHx: Hypertension
  Hyperlipidemia
  Diabetes mellitus
  Obesity
  Tobacco abuse
Case 1

- Physical exam:
  - BP 162/90 mm Hg, other vitals WNL
  - BMI 38
  - Truncal obesity, ↑ neck circumference
  - Retrognathia
Case 1

- Diagnostic PSG findings:
  - AHI 60/hour (obstructive)
  - REM AHI 100/hour
  - Arousal index 22/hour
  - SO2 nadir 74%
  - 50 minutes of TST with SO2 < 90%
  - 10% REM sleep
Case 1

- Patient had previously been intolerant of continuous positive airway pressure (CPAP)
- Now complaint of memory impairment and daytime hypersomnolence
- Neuropsychological testing confirmed impairments in vigilance and memory
Critical Questions

• Does OSAS increase risk of stroke?
  OSAS is associated with stroke (HR 2.24) (1)

• Can stroke cause OSA?
  Prevalence of OSAS in stroke patients is higher (2)

• Should every stroke patient undergo a screening sleep study?
  We don’t have data on this question

• What is causing this patient’s cognitive impairment?
  The big question?????

1) HK Yaggi etal, NEJM 2005
2) O Parra et al, AJRCCM, 2000
Proposed model for pathogenesis of CI in OSAS

Lal, C et al,
Chest 2012

OSAS

Static Risk Factors
- Age
- Gender
- Down’s syndrome
- ApoE4

Hypoxia

Inflammation

Endothelial dysfunction

Hormonal imbalance

Modifiable risk factors which also increase risk of OSAS
- Obesity
- Stroke
- CHF
- Psychoactive Drugs
- ETOH
- Smoking

Outcomes
- MCI
- Dementia

Impairment in:
- Executive function (including inductive and deductive reasoning)
- Vigilance
- Motor function

Modifiable risk factors associated with OSAS
- HTN
- Diabetes mellitus
- Metabolic syndrome
Significant regional decrease in gray matter of patients with OSAS rendered onto the brain surface of the mean of 42 registered brain images. Red shaded regions indicate areas of significant difference with decrease in the red intensity with increasing depth.

Brain changes with OSAS

Structural changes:
- Gray matter loss
- Hippocampal atrophy

Neurochemical changes:
- ↓ NAA/Choline
- Choline/Creatine
- Myoinositol level

Functional changes:
- Overactivation
- Underactivation

Role of Neuroimaging

NAA: N-acetyl aspartate
CI in OSAS

- Vigilance ++++ (1)
  - Variable effects on memory (4)
  - Increased Accident Risk
- Executive Function +++ (2)
- Motor Function ++ (3)
- Intelligence no effect

Increased Accident Risk

(1) Sforza E et al, ERJ, 2004; 24(2):279-285
(4) Beebe DW, Sleep 2003;26(3):298-307
Sleep Fragmentation

Excessive Daytime Sleepiness

CI

Partially Reversible with CPAP\(^{(1)}\)

Role of Modafinil/Armodafinil

\(^{(1)}\) Ferini-Strambi L et al, *Brain Res Bull* 2003
Critical Questions

• Should this patient be allowed to drive?
• What tests can be used in clinic to screen him for cognitive impairment?
### Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations? Answer considering how you have felt over the past week or so.

- 0 = Would never doze  
- 1 = Slight chance of dozing  
- 2 = Moderate chance of dozing  
- 3 = High chance of dozing

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<thead>
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<td>1. Sitting and reading</td>
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<td>2. Watching TV</td>
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<td>3. Sitting inactive in a public place (e.g., theater or meeting)</td>
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<td>4. As a passenger in a car for an hour without a break</td>
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<td>5. Lying down to rest in the afternoon when able</td>
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<td>6. Sitting and talking to someone</td>
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<td>7. Sitting quietly after a lunch without alcohol</td>
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<td>8. In a car while stopped for a few minutes in traffic</td>
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<td>MAYBE</td>
<td>YES</td>
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<td>1.</td>
<td>Compared to one year ago, do you feel that your memory has declined substantially?</td>
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<td>2.</td>
<td>Do others tell you that you tend to repeat questions over and over?</td>
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<td>Have you been misplacing things more often?</td>
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<td>4.</td>
<td>Do you find that lately you are relying more on written reminders?</td>
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<td>5.</td>
<td>Do you need more help from others to remember appointments, family occasions or holidays?</td>
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<td>6.</td>
<td>Do you have more trouble recalling names, finding the right word, or completing sentences?</td>
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<td>7.</td>
<td>Do you have more trouble driving?</td>
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<td>8.</td>
<td>Compared to one year ago, do you have more difficulty managing money?</td>
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<td>9.</td>
<td>Are you less involved in social activities?</td>
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<td>10.</td>
<td>Has your work performance declined significantly compared to one year ago?</td>
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<td>11.</td>
<td>Do you have more trouble following the news, or the plots of books, movies or TV shows, compared to one year ago?</td>
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<td>12.</td>
<td>Are there any activities that are substantially more difficult for you now compared to one year ago?</td>
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<td>13.</td>
<td>Are you more likely to become disoriented, or get lost, for example when traveling to another city?</td>
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<td>14.</td>
<td>Do you have more difficulty using household appliances?</td>
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<td><strong>MEAN SCORE</strong></td>
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Case 1

• Patient now agreed to try CPAP again
• Improvement in sleepiness and sustained attention seen after 6 months of compliant CPAP usage
• No improvement seen in memory
Case 2

- A 14 year old male patient with Down’s syndrome was evaluated by his pediatrician for significant developmental delay
- **PMHx**: Down’s syndrome
  - Hypothyroidism
  - Obesity
  - Hypertension
  - Snoring
Case 2

- Physical Exam: BP 164/94 mm Hg
  - Other vitals stable
  - Macroglossia
  - Adenotonsillar hypertrophy
  - ↑neck circumference
  - Truncal obesity
  - Flattened midface
Case 2

• Neuropsychological testing revealed learning disability, impairments in memory and attention

• Patient also had excessive daytime sleepiness with an Epworth sleepiness score (ESS) of 16
Case 2

- Diagnostic PSG findings:
  - AHI 80/hour (obstructive)
  - REM AHI 120/hour
  - SO2 nadir 54%
  - Arousal index 32/hour
Critical Questions

• How common is OSAS in Down’s syndrome patients?
• How common is cognitive impairment in Down’s syndrome?
OSAS in DS

- Prevalence of OSAS in DS children ranges from 30%-55% (1,2)
- OSAS prevalence increases in adults with DS (3)
- OSAS in DS patients is more severe than in the non-DS population

OSAS AND DS

• Adults with DS have a higher prevalence of dementia and Alzheimer’s Disease (1)

• OSAS can cause deficient visuoperceptual skills, including orientation, related to the right hemisphere in DS patients (2)

• DS children who snore are more likely to exhibit disruptive behaviour than DS children who don’t snore (3)

(3) Carskadon et al, Childs Nerv. Syst. 1993 Dec;9(8):452-7
Case 2

- Adenotonsillectomy was done
- Post-operative PSG revealed:
  - AHI 55/hour
  - REM AHI 82/hour
  - SO2 nadir 72%
  - Arousal index 24/hour
Case 2

- Improvement seen in ESS (=10)
- No improvements in memory, learning disability or attention
- Patient started on continuous positive airway pressure (CPAP) at 12 cm H2O based on a CPAP titration study
- Follow up nocturnal oximetry on CPAP showed no hypoxemia
A Randomized Trial of Adenotonsillectomy for Childhood Sleep Apnea

Carole L. Marcus, M.B., B.Ch., Reneé H. Moore, Ph.D., Carol L. Rosen, M.D., Bruno Giordani, Ph.D., Susan L. Garetz, M.D., H. Gerry Taylor, Ph.D., Ron B. Mitchell, M.D., Raouf Amin, M.D., Eliot S. Katz, M.D., Raanan Arens, M.D., Shalini Paruthi, M.D., Hiren Muzumdar, M.D., David Gozal, M.D., Nina Hattiangadi Thomas, Ph.D., Janice Ware, Ph.D., Dean Beebe, Ph.D., Karen Snyder, M.S., Lisa Elden, M.D., Robert C. Sprecher, M.D., Paul Willging, M.D., Dwight Jones, M.D., John P. Bent, M.D., Timothy Hoban, M.D., Ronald D. Chervin, M.D., Susan S. Ellenberg, Ph.D., and Susan Redline, M.D., M.P.H., for the Childhood Adenotonsillectomy Trial (CHAT)
Case 2

- ESS decreased to 6
- Repeat neuropsychological testing showed improvements in attention
- No improvements in memory or learning disability
Conclusions: Adults with DS frequently have OSAS, with obstructive apnea, hypoxemia, hypoventilation, and sleep fragmentation. We speculate that the complications of untreated OSAS (cardiovascular disease, increased mortality, and neurobehavioral morbidities including daytime sleepiness and impaired cognitive function) commonly overlap with the manifestations of DS.
Case 3

- A 66 years old male patient presented with diagnosis of Alzheimer disease (AD)
- **PMHx**: Hypertension
  - Congestive Heart Failure
  - Transient Ischemic Attacks
  - Diabetes mellitus
  - Snoring
  - Tobacco abuse (current smoker)
Case 3

• **Physical Exam**: BP 158/98 mm Hg
  Other vitals stable
  ↑neck circumference
  Obesity (BMI 32)
  Upper airway Mallampati IV

• **Mini-mental State Exam score**: 20
Case 3

• Neuropsychological testing revealed impairments in several cognitive domains
Case 3

• Diagnostic PSG findings:
  - AHI 45/hour (obstructive)
  - REM AHI 76/hour
  - SO2 nadir 78%
  - Arousal index 28/hour
Critical Questions

• Is cognitive impairment reversible with CPAP?
• Are some OSAS patients genetically predisposed to developing Mild Cognitive Impairment/AD?
- 17 treatment naïve OSAS patients
- 15 age-matched healthy controls
- Sleep study, cognitive tests and MRI
- Cognitive and imaging data collected after 3 months of CPAP treatment

Canessa N et al
*Am J Respir Crit Care Med* 2010
Case 3

- Apolipoprotein E (ApoE) genotyping revealed ApoE4/E4 homozygosity
- ApoE is a gene on chromosome 19
- ApoE carries instructions for forming a protein which helps to carry cholesterol in the bloodstream
- ApoE4 is seen in 25%-30% of the population and in 40% patients with late-onset AD

Farrer LA et al, JAMA. 1997
ApoE in OSAS and AD

• ApoE4 is associated with a higher risk of OSAS (OR 1.41, 95% CI 1.06-1.87, p = 0.02) especially in patients < 65 years of age (1)

• In a pediatric study, ApoE4 was found to occur more commonly in those children with OSAS who had low cognitive scores (2)

Case 3

- Patient started on CPAP at 10 cm H2O based on CPAP titration study
- Repeat cognitive testing after 3 months of CPAP, showed improvement in some domains including executive functioning and memory
- Patient tested positive for ApoE4 allele
Future Research Endpoints

- Neuroimaging biomarkers
  - Structural
  - Functional
  - Neurochemical

- Sleep Parameters
  - Sleep latency
  - REM sleep
  - Arousal Index
  - AHI/RDI
  - Sleep Efficiency

- Endothelial Biomarkers
  - EMP
  - EPC
  - Nitric Oxide
  - Prostacyclin
  - Endothelin-1
  - Thromboxane
  - ICAM-1, VCAM-1

EMP: Endothelial microparticle, EPC: Endothelial Progenitor cell, ICAM-1: Intercellular adhesion molecule, VCAM-1: Vascular cell adhesion molecule
Conclusion

• Neurocognitive decline in OSAS is a real and unique syndrome
• Impact of OSAS on cognitive decline is complicated by numerous co-morbidities
• Further studies are required to translate emerging findings in this area to the clinical setting