The Interface Between Sleep Apnea and Seizures

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What is Sleep Apnea?

• Obstructive sleep apnea syndrome (OSA) is characterized by repeated upper airway obstructions leading to oxygen desaturations and sleep fragmentation.

• Important consequences include such as excessive daytime sleepiness and a higher risk of cerebrovascular or cardiovascular disease.

• Snoring is the most common symptom and obesity the most important risk factor.
What is a Seizure?

• An epileptic seizure has been defined by the International League Against Epilepsy (ILAE) as “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain”.

• Sleep deprivation can exacerbate seizures and seizures can cause sleep fragmentation.

• Generalized convulsions can lead to hypoxia.
How Common is OSA in Epilepsy.

- Thirty nine subjects without past history of OSA but with refractory partial epilepsy underwent PSGs.
- 13/39 had OSA as defined as sleepiness and/or hypertension and an AHI of >5 or an AHI >15.
- 5/39 had severe OSA defined as AHI>30/hour.
- More common in older men and those with nocturnal seizures.

Malow et al Neurology 2000
How Common is OSA in Epilepsy.

• 238 subjects without past history of OSA but with epilepsy underwent portable studies and structured interviews.
• Coexistence of OSA with epilepsy was found in 24 or 10.2% (15.4% of the male and 5.4% of the female).
• Three or 11.1% had severe OSA
• More common those who experienced seizures at an older age.

Manni et al Epilepsia 2003
How About in Children?

- Twenty six subjects without past history of OSA or any neurological or psychiatric disorder but with epilepsy underwent PSG.
- OSA found in 11 or 42.3%.
- Those with OSA had a higher seizure frequency.

Shaheen et al Sleep Breath 2012
How About in Children?

- 84 children with epilepsy.
- 52 classified as mild and 32 as severe.
- 44% of severe group vs. 31% of mild group had OSA.
- More AEDs meant higher chance of OSA.
- No correlation with seizure type.
The Facts.

- Fourteen patients compliant on CPAP for 3 months.
- All had moderate to severe OSA.
- No change in AEDs.
- All partial seizures.
- 5/14 improved in seizures and sleepiness.

Malow et al Neurology 1997
The Facts.

• Four patients with refractory epilepsy and moderate OSA compliant with CPAP.
• At 6 months and 2 years there is an overall >50% reduction in seizures without AED change with half the patients being completely seizure free.

Beran et al Seizure 1997
The Facts.

• 6/13 adults had OSA and refractory epilepsy with at least one seizure a week
• 3/5 children had OSA and refractory epilepsy with at least one seizure a week.
• All treated with CPAP or oral appliance.
• 1/3 children tolerated CPAP and had >50% reduction in seizures.
• 3/6 adults on CPAP and 1/6 on oral appliance also had >50% reduction in seizures.

Mallow et al Sleep Med 2003
The Facts.

• 557 patients with OSA out of whom 29 have epilepsy (5%).
• 21 had worsening of seizures at the time of diagnosis with OSA.
• 23 were given CPAP
• 12 compliant
• 4 out of 12 had significant reduction in seizures.
• Take home message: OSA much more prevalent in epilepsy population than epilepsy in OSA population.

Hollinger Eur Neurol. 2006
The Facts.

• Forty one patients with moderate OSA and epilepsy (average 2 seizures/month).
• Twenty eight CPAP compliant and 13 non compliant.
• No difference in the number of AEDs or seizure severity between the compliant and non compliant groups.
The Facts.

- Stable AEDs over 6 months.
- At 6 month follow up 16/28 on CPAP were seizure free and only 2/13 not on CPAP were seizure free.
- Overall seizures decreased from 2 to 1/month in CPAP group and remained the same in non CPAP group

Vendrame et al Epilepsia 2011
The Facts.

- Assessed for eligibility (n=865)
  - Excluded (n=797)
    - Not meeting inclusion criteria (n=778)
    - Declined to participate (n=3)
    - Other reasons (n=16)
  - Enrollment (n=8)
    - Excluded (n=23)
      - Screen failure (n=6)
      - Voluntary withdrawal (n=2)
      - Lost to follow-up (n=7)
      - Other (n=8)
  - Underwent PSGs (n=45)
    - Did not have OSA on PSG (n=9)
    - Not randomized per physician decision (n=1)
- Randomized (n=35)
  - Allocated to therapeutic CPAP (n=22)
    - All received allocated intervention
      - Discontinued intervention (n=3)
        - Unable to tolerate CPAP (n=2)
        - Change in medications (n=1)
        - None lost to follow-up
      - Analyzed (n=19)
  - Allocated to sham CPAP (n=13)
    - All received allocated intervention
      - Discontinued intervention (n=0)
      - None lost to follow-up
      - Analyzed (n=13)

Graph:
- Apnea-hypopnea index
- sham CPAP vs therapeutic CPAP
- Baseline study vs Titration study

Malow et al Neurology 2008
The Facts (You Decide).

• A 50% or greater reduction in seizures was observed in 28% of the subjects in the therapeutic group as compared to 15% of those in the sham group.

• This result was not statistically significant ($p = 0.40$).

• Four subjects treated with therapeutic CPAP and one subject treated with sham CPAP became seizure-free.

Malow et al. Neurology 2008
Who is more likely to have OSA?

- Two groups of adults with epilepsy underwent PSGs.
- Group 1 (11) had more, later onset and worsening seizures.
- Group 2 (10) had controlled or significantly less seizures.
- 5/11 on CPAP.
- 3/5 resolution or significant improvement in seizures.

Chihorek et al Neurology 2007
Who is more likely to have OSA?

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of subjects with late-onset or worsening seizures (Group 1) and those who were seizure-free or who had improvement of seizures (Group 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1, n = 11</td>
</tr>
<tr>
<td>Apnea-hypopnea index</td>
<td>23.2 (26.2)</td>
</tr>
<tr>
<td>SA-SDQ score</td>
<td>16.3 (4.1)</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score</td>
<td>11.6 (3.6)</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.0 (9.7)</td>
</tr>
<tr>
<td>Men</td>
<td>82%</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.6 (5.3)</td>
</tr>
<tr>
<td>Neck circumference, in</td>
<td>16.1 (1.5)</td>
</tr>
<tr>
<td>No. of antiepileptic drugs</td>
<td>1.5 (0.5)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>45.4%</td>
</tr>
<tr>
<td>Nocturnal seizures predominantly</td>
<td>2</td>
</tr>
</tbody>
</table>

Values presented as mean (SD).
SA-SDQ = Sleep Apnea section of the Sleep Disorder Questionnaire.
The Twist.

• 130 subjects with OSA and epilepsy.
• BMI and gender not strong predictors of OSA in epilepsy in a regression analysis.
• Number of AEDs, poor dentition and age were.
• Take home message: look for OSA in patients with severe epilepsy even if they are thin women.

Foldvary-Schaefer et al Epilepsy Behav. 2012
What Else Does OSA Worsen?

- 124 epilepsy patients evaluated for sleep problems.
- 35/124 or 28.2% have OSA.
- Quality of Life is much worse in those who have OSA vs. those who don’t.
- Insomnia without OSA also worsens quality of life of patients with epilepsy independent of seizures.
The Odd One Out?

- 18 year old woman with epilepsy and OSA
- Evaluated right after CPAP initiation and 4 months after with a full EEG sleep study.
- No change in seizures which were pretty well controlled.
Possible Mechanisms?

• Sudden increase in Slow Wave or N3 sleep.
• Changes in cerebral blood flow.
• In this particular case she also had sudden decrease in REM when using CPAP initially with recovery after 4 months.

197 patients with epilepsy out of which 30 (15.2%) had OSA.

15 compliant with CPAP.

12 seizure free (2 became seizure after CPAP and other interventions), 3 significant improvement.

In addition to being predominantly male and older than those without OSA there was also a higher prevalence of diabetes.

Li et al Seizure 2012
How Can OSA Worsen Epilepsy?

• Increasing arousals during NREM sleep
• Inducing daytime sleepiness

Manni et al Epilepsy Res 2010
How Can OSA Worsen Epilepsy?

• Cognitive problems attention, planning and spatial learning are common in epilepsy and in OSA but OSA tends to worsen these in subjects with epilepsy.

• Possible hypoxemia but most OSA patients whose epilepsy improved with CPAP did not desaturate below 87%
How Can Epilepsy Worsen OSA?

• 18 year old patient with OSA and intractable epilepsy.
• Undergoes resective surgery.
• Both seizures and OSA resolve without any change in weight.

Foldvary-Schaefer et al  Epilepsia 2008
How Can Epilepsy Worsen OSA?

• Worsening of sleep apnea transiently has been reported in patients immediately following a nocturnal frontal lobe seizure.
• Hypoxemia and transient sleep apnea has been reported in temporal lobe seizures.
• Possibly increased electrical discharges affect brain stem structures and cause apneas.

Manni et al Epilepsy Res 2010
How Can Epilepsy Worsen OSA?

• It is possible that cessation of seizures and reduction of interictal discharges stabilize sleep thereby reducing respiratory events.

• Or abundant interictal discharges and/or seizures, as observed in this case, adversely affect upper airway control during sleep in vulnerable patients.
How do epilepsy treatments cause OSA?

• Vagal nerve stimulator (VNS) elevated AH1 from <5/hour (normal) to 12/hour in 5/16 patients.

• Apneas & hypopneas occur more frequently during VNS activation than during non-activation.

• Lowering stimulus frequency, but not intensity, pulse width, or on-time, ameliorates VNS-related apneas and hypopneas

Marzec et al Epilepsia 2003
Could this partially explain SUDEP?
VNS and OSA in Children.

• Twenty six children with severe epilepsy implanted with VNS.
• Four or 15% developed mild or moderate OSA after VNS was activated.
• Three underwent tonsillectomy and adenoidectomy and had resolution of OSA and 1 had resolution of seizures.
• 1 had repeat adenoidectomy and CPAP.
• The remaining 3 had significant reduction in seizures after OSA treatment.
How do epilepsy treatments cause OSA?

- Stimulation of peripheral vagal neurons may alter neuromuscular transmission to the upper airway muscles of the pharynx and larynx producing upper airway narrowing and obstruction.

- VNS may also affect brainstem reticular formation altering the rate and depth of respiration.

Marzec et al. Epilepsia 2003

Vendrame et al. Epilepsia 2011
How do epilepsy treatments cause OSA?

- Weight gain.
- Majority of AEDs have weight gain as a prominent side effect and rapid weight gain leads to OSA.
- Sodium Valproate or Valproic Acid can also induce Polycystic Ovarian Syndrome in women (PCOS) which dramatically increases the risk of OSA.
- Some sedative meds can depress respiratory drive and decrease muscle tone in upper airway

Manni et al Epilepsy Res 2010
In Conclusion.

- OSA is prevalent in epilepsy populations.
- 10-30% vs. 4%
- Epilepsy is common in OSA 5% vs 1%
- Both can worsen each other.
- Treating OSA significantly improves seizures.
- Treating seizures may improve OSA.