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Diagnosing And Treating Co-Morbid Sleep Apnea In Neurological Disorders

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Obstructive sleep apnea (OSA) is an extremely common public health problem manifested by sleep-disordered breathing, daytime hypersomnia and poor sleep quality, adverse neurocognitive sequelae, and hypoxia. OSA occurs in about two-four percent of the general population, or an estimated 18 million Americans.1 Co-morbid OSA is even more frequent in neurological patients, affecting at least one-third of those with epilepsy and about two-thirds of stroke survivors. Just as effective treatment of OSA may improve hypertensive control and reduce risk of cardiovascular complications, there is now growing evidence that treating co-morbid OSA also improves neurological outcomes such as cognitive functioning and seizure control. Since neurologists frequently serve as principal care providers for those with epilepsy, stroke, multiple sclerosis, and migraine, it is crucial for neurology physicians to be familiar with the identification of sleep apnea early in its presentation to provide optimal care for their patients. This article reviews the typical common clinical manifestations of obstructive sleep apnea and its adverse impact on neurocognitive functioning, focuses on the influence of co-morbid OSA on selected neurological disorders, and provides some concluding practical pointers on the diagnosis and treatment of OSA for practicing neurologists.

OSA and The Spectrum of Sleep Disordered Breathing

Obstruction of the upper airway during sleep causes a continuum of breathing disturbances, varying from mild snoring, to partial airway obstruction causing a heightened respiratory effort necessary to preserve airflow and oxygenation, thereby leading to arousal (a respiratory effort related arousal, or RERA), to airflow limitation (hypopnea), and to cessation of airflow (apnea). Some patients have a typical predisposing anatomy of a narrowed oropharynx. Anatomical factors at the level of the nose, nasopharynx, oropharynx, or hypopharynx may all predispose, and most adult patients have multi-level obstructive factors. Common anatomical factors increasing vulnerability towards OSA include nasal septal deviation, polyps, a low-lying palate or redundant soft palatal tissue, a thickened tongue base, or a narrow hypopharynx.

The mildest form of upper airway obstructive sleep disordered breathing is snoring. Snoring results from narrowing in the nasal passages or oropharynx significant enough to produce turbulent airflow, leading to vibration of the soft palatal tissue. Primary snoring is diagnosed when no other disturbance in sleep or respiration is found during polysomnography. While snoring has been correlated with risk of hypertension, primary snoring is basically otherwise benign except for its disruptive effects on the sleep of bedpartners or roommates.

Since neurologists are frequently principal care providers for many neurological patients, it is crucial for neurology physicians to be familiar with the identification of sleep apnea. First of a two part series.

Typical historical features of OSA include loud disruptive snoring, snort arousals, witnessed apneas, and excessive daytime sleepiness. OSA is associated with development of hypertension and is a risk factor for stroke, coronary artery disease, congestive heart failure, and atrial fibrillation. OSA disrupts endothelial and metabolic homeostasis, mediating an increased risk of atherosclerotic vascular disease. Untreated moderately severe or severe OSA patients have an increased risk of mortality and adverse cardiovascular and cerebrovascular events.

OSA severity is determined during polysomnography by the apnea-hypopnea index (AHI), the hourly rate of apneas and hypopneas during sleep. Severity of OSA, according to AHI, is as follows: normal=4 or fewer events/hour; mild=5–14 events/hour; moderate=15–29 events/hour; and severe=30 per hour or higher. The AHI is further correlated with specific sleep stages and body positions to determine whether positional therapy can be offered, since many patients have OSA only during supine sleep (i.e., position-dependent OSA).

Upper airway resistance syndrome (UARS) is the mildest variant of OSA. UARS is characterized by snoring, frequent snort arousals, and daytime hypersomnia, but without an abnormally high frequency of overt apneas or hypopneas. Polysomnography demonstrates frequent, repetitive respiratory effort related arousals (RERAs), generally at a frequency of 10 or more per hour.

Central sleep apnea (CSA) results from reduced ventilatory drive during sleep that causes episodic insufficient ventilation and compromised gas exchange despite oropharyngeal airway patency. Insomnia is a more frequent complaint in CSA patients than hypersomnia, and snoring is generally less dramatic. CSA may be idiopathic or due to a variety of other causes including high altitude periodic breathing, Cheynes-Strokes respirations, narcotic medications, or primary neurological causes such as brainstem infarction or multiple systems atrophy. CSA is often refractory to treatment with nasal CPAP therapy, which may improve oxygenation but fail to improve frequent spontaneous arousals that fragment sleep. Alternative PAP modalities such as adaptive servoventilation (ASV) may be superior for CSA treatment.

Complex sleep apnea syndrome (CompSAS) is characterized by predominant or exclusive OSA at baseline that evolves during the course of CPAP therapy to occurrence of frequent central apneic events that may or may not resolve after ongoing home use of CPAP. CompSAS patients with continued central apneic events at a frequency of five or more per hour often have persisting clinical complaints of hypersomnia and continued medical risk despite an otherwise favorable response to CPAP treatment. CompSAS occurs in approximately four-15 percent of OSA patients. As in CSA therapy, ASV may be superior to conventional CPAP for treatment of compSAS.

Sleep-related hypoventilation (SRH) differs from sleep apnea since there is an enduring, longitudinal failure of ventilation to produce adequate oxygenation during sleep over a time course of several minutes (vs. a time frame of seconds to a half-minute or so in sleep apnea syndromes). SRH is most often caused by primary pulmonary disorders, neuromuscular bellows failure, or restrictive chest wall movement from obesity or kyphoscoliotic disorders. These disorders may cause daytime hypoventilation but frequently evolve SRH earlier due to sleep-related vulnerability factors such as supine sleep positioning and REM stage sleep that lead to relative chest wall paralysis and dependency on diaphragmatic breathing. SRH may mediate medical risk via polycythemia, pulmonary hypertension and right heart failure, or hypercapnic respiratory failure. SRH therapy necessitates non-invasive positive pressure ventilation, in most instances titrated during polysomnography. One should strictly avoid simply adding oxygen therapy alone in certain common etiologies of SRH including severe

COPD or neuromuscular disorders, since hypercapnea occurs during chronic respiratory failure and the hypoxic drive to breathe becomes predominant in this context. Because the chronically hypoventilating patient has become reliant on hypoxia to drive breathing, masking the hypoxic breathing drive with oxygen therapy alone can actually precipitate acute respiratory failure in some individuals. A morning arterial blood gas on room air following polysomnography is indicated to assess for potential hypercapnea and assess the impact of ventilatory support. When there is severe hypercapnea with pCO2 of 55 torr or higher, serial arterial blood gases are necessary to carefully monitor the impact of bilevel PAP ventilatory support, since nocturnal mechanical ventilation may be necessary when hypercapnea increases due to failing ventilatory efforts.

OSA-Related Neurocognitive Impairment

OSA causes cessation of airflow with resulting hypoxia and mircoarousals that fragment sleep, leading to nonrestorative sleep and reduced daytime functioning from sleepiness and cognitive impairment. OSA-related sleep fragmentation causes significant morbidity due to impaired daytime functioning, quality of life, and driving safety.2 Daytime dysfunction includes hypersomnia, attentional impairments, and executive dysfunction.3–5

OSA-related cognitive impairments are common and broad, including speed of information processing, attention and working memory, executive functioning, learning and memory, alertness and sustained attention, visuospatial learning, motor performance, and constructional abilities, but OSA largely spares global cognitive functioning and language. 3–6 Attentional impairments in adult OSA patients are comparable to the effects of alcohol intoxication.7 In children with OSA, a clinical state mimicking attention-deficit hyperactivity disorder (ADHD) often occurs, including inattention, impulsivity, hyperactivity, and aggression. Vigilance impairments may be enduring or more momentary, with microsleeps mimicking inattention or lapses in concentration; deterioration in driver control over vehicle position and steering has been shown to occur during microsleep episodes in drivers with OSA.8 OSA increases crash risk by two-to-three fold, irrespective of sleepiness or apnea severity.9 Sleep fragmentation, hypoxia, or both may mediate these impairments.6

The course of OSA-related deficits following treatment with nasal continuous positive airway pressure (CPAP) is variable, but improvements in vigilance, attention, and reaction time are expected. Treatment with CPAP reduces subsequent crash risk in commercial drivers by 72 percent, toward a level approaching the background rate in the general population.10 However, several structural, functional, and magnetic resonance spectroscopic neuroimaging studies in treated OSA patients have shown signs of persistent hippocampal, dorsolateral prefrontal, cingulate, and posterior parietal neural damage despite nasal CPAP treatment, suggesting that identification and treatment of OSA should be regarded as a public health imperative to prevent permanent, irreversible cognitive sequelae of OSA.5,11–12

Co-Morbid OSA in Neurological Disorders

The importance of treating co-morbid OSA in a variety of neuropsychiatric disorders has been steadily gaining increased recognition, and the spectrum of neurological disorders with primary neurological symptoms reported to improve by treatment of underlying comorbid sleep apnea now includes dementia, stroke, epilepsy, and headache,13–15 and sleep disordered breathing is quite common in patients with neuromuscular disorders.

Dementia

There has been rich speculation that untreated OSA may be a risk factor for evolution of dementia, although a recent large community-based study suggested only negligible influence of moderate or severe OSA on cognitive function.16–17 The APOE4 allele is associated with both an increased risk of evolving OSA and Alzheimer's disease.18–19 One small, recent study found that APOE4 genotype conferred a higher risk of memory impairments in older adults with OSA, but as of yet there has been no conclusive evidence of an increased risk of future dementia in those with OSA.20 Curiously, a recent clinical trial in Alzheimer's disease and co-morbid OSA suggested that donepezil improves both OSA severity and cognitive performance.21

Symptoms of disordered sleep are common even in those with incipient dementia, with insomnia and hypersomnia occurring in 20–30 percent of patients. Between 30–70 percent of those with Alzheimer's disease have sleep-disordered breathing.22 Evidence is conflicting on whether CPAP treatment of co-morbid OSA in Alzheimer's disease patients improves cognition, although improvements in sleep quality, daytime sleepiness, and mood appear consistent.13,23–26 It remains unclear whether patients with Alzheimer's disease are able to adequately adhere to CPAP therapy, but a recent study found comparable rates of adherence in non-depressed Alzheimer patients to those of cognitively normal patients.27 Larger confirmatory controlled trials of the feasibility, adherence, and efficacy of CPAP for treatment of co-morbid OSA in Alzheimer's disease are needed to further clarify these observations given conflicting evidence, but until further definitive evidence becomes available, offering treatment with CPAP to patients who are able to comply is certainly reasonable.

Alzheimer patients frequently also suffer from other co-morbid sleep disorders, including insomnia, disturbed chronobiology with advanced sleep phase or non-entrained circadian disturbances of sleep periods, periodic limb movement disorder, a central hypersomnia similar to narcolepsy, and REM sleep behavior disorder. Treatment of sleep disordered breathing often helps reduce the burden of symptoms from these other sleep problems.

Between 20–50 percent of patients with Diffuse Lewy Body Disease or Parkinson's Disease manifest hypersomnia, and approximately 20 percent of these patients have OSA.28 Patients with parkinsonism often derive significant benefits in daytime alertness and overall functioning with treatment of co-morbid OSA, although direct neurological benefits on cognitive and motor functioning are less clear-cut.29 Patients with parkinsonism, particularly those with Lewy Body Dementia, are also vulnerable to have a narcolepsy-like enduring hypersomnia despite treatment of OSA, so that treatment with adjunctive modafanil may be necessary to relieve hypersomnia in some individuals,28 and REM sleep behavior disorder is commonly seen in those with parkinsonism, requiring additional treatment with melatonin or clonazepam in many cases to prevent injury to the patient or bed partner.

Stroke

OSA raises the risk for stroke and appears to reduce favorable outcomes from completed stroke, probably via multiple factors such as the impact of direct neural injury or extension of vascular penumbra via repetitive hypoxia and ischemia due to apneic events, worsened hypertension via autonomic activation, and vascular endothelial effects favoring atherothrombosis. CPAP adherence in stroke survivors is often difficult given neurological deficits that confound its use.30 Since OSA is a treatable risk factor for stroke and a factor in its outcome, identification and early treatment of OSA are theorized to be helpful in both the primary and secondary prevention of cerebrovascular disease, although there are as yet

no definitive prospective controlled trial data demonstrating that treatment of OSA lowers stroke risk.30 Since most stroke patients spend the majority of their time in bed in the supine position, a recognized precipitant of increased apnea severity, some experts have suggested that positional therapy may be a reasonable treatment alternative in the acute setting and this approach certainly warrants future formal prospective research.31

Epilepsy

Patients with epilepsy appear to have more frequent co-morbid OSA than the general population, leading to hypersomnia, worsened seizure frequency, and added health risk.32 Co-morbid OSA may worsen seizure control, particularly increasing the risk of nocturnal seizure burden, by mediating sleep disruption and deprivation. Epilepsy patients who have OSA are more often older, heavier, and male.32–33 Treatment of co-morbid OSA with nasal continuous positive airway pressure therapy (nCPAP) may provide several benefits to those with epilepsy, including reduction in apnea-hypopnea index (AHI), reduced daytime sleepiness, and improvements in seizure frequency.32–34

Headache

While headache is a relatively common symptom in OSA, and co-morbid OSA can aggravate frequency and severity of habitual headaches in migraineurs, there has been surprisingly little formal scrutiny of the impact of OSA on headache disorders. Sleep and headache may be related in several ways, in that primary headache disorders such as migraine, cluster, and hypnic headache can be aggravated or triggered by sleep and sleep disorders, while chronic daily headaches in the morning hours upon awakening are commonly associated with OSA.35–36 A history of OSA should be especially sought in those with cluster headache, given that OSA treatment has been recently shown to reduce cluster headache frequency.15 While not directly associated, treatment of OSA may occasionally also be helpful in elderly patients with hypnic headache (“alarm clock headache”) is a distinctive sleep-related migrainoid headache disorder characterized by frequent headaches arising directly from sleep within a few hours after bedtime, and typically although not invariably arising from stage REM.

Neuromuscular disorders

Motor neuron disease, myasthenia gravis, and myopathies have been associated with prominent sleep disordered breathing. OSA is especially frequent in myotonic dystrophy Type 1 (DM1), seen in up to 70 percent of patients, and DM1 patients may also have symptomatic narcolepsy with prominent hypersomnia.37–39 Patients with neuromuscular disorders, especially those with myopathy or motor neuron disease, may evolve sleep related hypoventilation with bellows failure, and usually initially manifest hypoventilation during sleep, especially during stage REM. Screening these patients with home overnight portable oximetry monitoring can be very helpful in identifying mild early respiratory insufficiency and implementing appropriate supportive non-invasive positive pressure ventilation during sleep.

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References

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993; 328:1230–1235. [PubMed: 8464434]
2. Verstraeten E. Neurocognitive effects of obstructive sleep apnea syndrome. Curr Neurol Neurosci Rep. 2007; vol. 7(no. 2):161–166. [PubMed: 17324368]
3. Aloia MS, Arnedt JT, Davis JD, Riggs RL, Byrd D. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome. J Intl Neuropsych Soc. 2004; 10:772–785.
4. St. Louis EK. Error detection is impaired in obstructive sleep apnea syndrome. Sleep. 2009; 32 Suppl:A420.
5. Beebe DW, Groesz L, Wells C, Nichols A, McGee K. The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case-controlled data. Sleep. 2003; 26(3):298–307. [PubMed: 12749549]
6. Quan SF, Wright R, Baldwin CM, Kaemingk KL, Goodwin JL, Kuo TF, Kaszniak A, Boland LL, Caccappolo E, Bootzin RR. Obstructive sleep apnea-hypopnea and neurocognitive functioning in the Sleep Heart Health Study. Sleep Med. 2006; 7:498–507. [PubMed: 16815753]
7. Powell NB, Schechtman KB, Riley RW. The road to danger: the comparative risks of driving while sleepy. Laryngoscope. 2001; 111:887–893. [PubMed: 11359171]
8. Boyle LN, Tippin J, Paul A, Rizzo M. Driver performance in the moments surrounding a microsleep. Transp Res Part F Traffic Psychol Behav. 2008; 11(2):126–136. [PubMed: 20090864]
9. Ellen RLB, Marshall SC, Palayew M, Molnar FJ, Wilson KG, Man-Son-Hing M. Systematic review of motor vehicle crash risk in persons with sleep apnea. J Clin Sleep Med. 2006; 2:193. [PubMed: 17557495]
10. Tregear, S. Obstructive sleep apnea and commercial motor vehicle driver safety: findings of evidence report. 2007. accessed on world wide web at: http://www.mrb.fmcsa.dot.gov/documents/PPP/OSA_Evidence_Report_Tregear.pdf
11. Ayalon L, Ancoli-Israel S, Aka AA, McKenna BS, Drummond SP. Relationship between obstructive sleep apnea severity and brain activation during a sustained attention task. Sleep. 2009; 32(3):373–381. [PubMed: 19294957]
12. Ayalon L, Peterson S. Functional central nervous system imaging in the investigation of obstructive sleep apnea. Curr Opin Pulm Med. 2007; 13(6):479–483. [PubMed: 17901752]
13. Ancoli-Israel S, Palmer BW, Cooke JR, Corey-Bloom J, Fiorentino L, Natarajan L, Liu L, Ayalon L, He F, Loredo JS. Cognitive effects of treating obstructive sleep apnea in Alzheimer's disease: a randomized controlled study. J Am Geriatr Soc. 2008; 56(11):2076–2081. [PubMed: 18795985]
14. Malow BA, Foldvary-Schaefer N, Vaughn BV, Selwa LM, Chervin RD, Weatherwax KJ, Wang L, Song Y. Treating obstructive sleep apnea in adults with epilepsy: a randomized pilot trial. Neurology. 2008; 71(8):572–577. [PubMed: 18711110]
15. Nath Zallek S, Chervin RD. Improvement in cluster headache after treatment for obstructive sleep apnea'. Sleep Med. 2000; 1(2):135–138. [PubMed: 10767655]
16. Abrams B. Add Alzheimer's to the list of sleep apnea consequences. Med Hypotheses. 2005; 65(6): 1201–1202. [PubMed: 16085367]
17. Sforza E, Roche F, Thomas-Anterion C, Kerleroux J, Beauchet O, Celle S, Maudoux D, Pichot V, Laurent B, Barthélémy JC. Cognitive function and sleep related breathing disorders in a healthy elderly population: the SYNAPSE study. Sleep. 2010; 33(4):515–521. [PubMed: 20394321]
18. Bliwise DL. Sleep apnea, APOE4 and Alzheimer's disease 20 years and counting? J Psychosom Res. 2002; 53(1):539–546. [PubMed: 12127169]
19. Gottlieb DJ, DeStefano AL, Foley DJ, Mignot E, Redline S, Givelber RJ, Young T. APOE E4 is associated with obstructive sleep apnea/hypopnea. Neurology. 2004; 63:664–668. [PubMed: 15326239]
20. O'Hara R, Schröder CM, Kraemer HC, Kryla N, Cao C, Miller E, Schatzberg AF, Yesavage JA, Murphy GM Jr. Nocturnal sleep apnea/hypopnea is associated with lower memory performance in APOE epsilon4 carriers. Neurology. 2005; 65(4):642–644. [PubMed: 16116137]

21. Moraes W, Poyares D, Sukys-Claudino L, Guilleminault C, Tufik S. Donepezil improves obstructive sleep apnea in Alzheimer disease: a double-blind, placebo-controlled study. Chest. 2008; 133(3):677–683. [PubMed: 18198262]
22. Rongve A, Boeve BF, Aarsland D. Frequency and correlates of caregiver-reported sleep disturbances in a sample of persons with early dementia. J Am Geriatr Soc. 2010; 58(3):480–486. [PubMed: 20398116]
23. Chong MS, Ayalon L, Marler M, Loredo JS, Corey-Bloom J, Palmer BW, Liu L, Ancoli Israel S. Continuous positive airway pressure reduces subjective daytime sleepiness in patients with mild to moderate Alzheimer's disease with sleep disordered breathing. J Am Geriatr Soc. 2006; 54(5): 777–781. [PubMed: 16696743]
24. Cooke JR, Ancoli-Israel S, Liu L, Loredo JS, Natarajan L, Palmer BS, He F, Corey-Bloom J. Continuous positive airway pressure deepens sleep in patients with Alzheimer's disease and obstructive sleep apnea. Sleep Med. 2009; 10(10):1101–1106. [PubMed: 19699148]
25. Cooke JR, Ayalon L, Palmer BW, Loredo JS, Corey-Bloom J, Natarajan L, Liu L, Ancoli-Israel S. Sustained use of CPAP slows deterioration of cognition, sleep, and mood in patients with Alzheimer's disease and obstructive sleep apnea: preliminary study. J Clin Sleep Med. 2009; 5(4): 305–309. [PubMed: 19968005]
26. Frohnhofen H, Heuer HC, Kanzia A, Firat A. Influence of type of treatment for sleep apnea on activities of daily living in a sample of elderly patients with severe sleep apnea. J Physiol Pharmacol. 2009; 60 suppl 5:51–55. [PubMed: 20134039]
27. Ayalon L, Ancoli-Israel S, Stepnowsky C, Marler M, Palmer BW, Liu L, Loredo JS, Corey-Bloom J, Greenfield D, Cooke J. Adherence to continuous positive airway pressure treatment in patients with Alzheimer's disease and obstructive sleep apnea. Am J Geriatr Psychiatry. 2006 Feb; 14(2): 176–180. [PubMed: 16473983]
28. Arnulf I. Excessive daytime sleepiness in parkinsonism. Sleep Med Rev. 2005; 9(3):185–200. [PubMed: 15893249]
29. Rye DB. Excessive daytime sleepiness and unintended sleep in Parkinson's disease. Curr Neurol Neurosci Rep. 2006 Mar; 6(2):169–176. [PubMed: 16522272]
30. Dyken ME, Im KB. Obstructive sleep apnea and stroke. Chest. 2009; 136:1668–1677. [PubMed: 19995768]
31. Brown DL, Lisabeth LD, Zupancic MJ, Concannon M, Martin C, Chervin RD. High prevalence of supine sleep in ischemic stroke patients. Stroke. 2008; 39:2511–2514. [PubMed: 18617656]
32. Malow BA, Levy K, Maturen K, Bowes R. Obstructive sleep apnea is common in medically refractory epilepsy patients. Neurology. 2000; 55(7):1002–1007. [PubMed: 11061259]
33. Manni R, Terzaghi M, Arbasino C, Sartori I, Galimberti CA, Tartara A. Obstructive sleep apnea in a clinical series of adult epilepsy patients: Frequency and features of comorbidity. Epilepsia. 2003; 44(6):836–840. [PubMed: 12790898]
34. Malow BA, Foldvary-Schaefer N, Vaughn BV, Selwa LM, Chervin RD, Weatherwax KJ, Wang L, Song Y. Treating obstructive sleep apnea in adults with epilepsy: a randomized pilot trial. Neurology. 2008; 71(8):572–577. [PubMed: 18711110]
35. Alberti A. Headache and sleep. Sleep Med Rev. 2006; 10:431–437. [PubMed: 16872851]
36. Rains JC, Poceta JS. Headache and sleep disorders: review and clinical implications for headache management. Headache. 2006; 46:1344–1363. [PubMed: 17040332]
37. Laberge L, et al. Sleep Complaints in Patients with Myotonic Dystrophy. J. Sleep Res. 2004; 13:95–100. [PubMed: 14996041]
38. Laberge L, et al. A Polysomnographic Study of Daytime Sleepiness in Myotonic Dystrophy Type 1. JNNP. 2009; 80:642–646.
39. Phillips MF, et al. Daytime Somnolence in Myotonic Dystrophy. J. Neurol. 1999; 246:275–282. [PubMed: 10367695]