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Obstructive sleep apnea is associated with seizure occurrence in older adults with epilepsy



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ABSTRACT

Background: Although epileptic seizures occur more commonly in older adults, their occurrence in this age group is often unexplained. One unexplored precipitant of seizures in older adults is obstructive sleep apnea (OSA), which is also more common in this age group. Our objective was to investigate whether OSA is associated with seizure exacerbation in older adults with epilepsy.

Methods: Polysomnography was performed in older adult patients with late-onset or worsening seizures (Group 1, $n = 11$) and those who were seizure-free or who had improvement of seizures (Group 2, $n = 10$).

Results: Patients in Group 1 had a significantly higher apnea-hypopnea index than patients in Group 2 ($p = 0.002$). Group 1 patients also had higher Epworth Sleepiness Scale scores ($p = 0.009$) and higher scores on the Sleep Apnea Scale of the Sleep Disorders Questionnaire ($p = 0.04$). The two groups were similar in age, body mass index, neck circumference, number of antiepileptic drugs currently used, and frequency of nocturnal seizures.

Conclusions: Obstructive sleep apnea is associated with seizure exacerbation in older adults with epilepsy, and its treatment may represent an important avenue for improving seizure control in this population. *Neurology*® 2007;69:1823-1827

GLOSSARY

AED = antiepileptic drug; **AHI** = apnea-hypopnea index; **CPAP** = continuous positive airway pressure; **EDS** = excessive daytime sleepiness; **ESS** = Epworth Sleepiness Scale; **OSA** = obstructive sleep apnea; **PSG** = polysomnography; **SA-SDQ** = Sleep Apnea section of the Sleep Disorder Questionnaire.

Although the incidence of new-onset seizures is much higher in the older adult population than in any other age group, their etiology remains unknown in approximately 45% of individuals.¹ Obstructive sleep apnea (OSA), a sleep disorder which becomes more common with increasing age, is one unexplored potential etiologic or precipitating factor in patients without an established cause (e.g., stroke, tumor, degenerative disease). The presence of untreated OSA can lead to sleep fragmentation and chronic sleep deprivation, which may facilitate seizures in susceptible individuals.²⁻⁴

As a first step to determine whether OSA may be a cause of seizures in older adults, we performed a cross-sectional study of all older adults presenting to a tertiary center epilepsy clinic to determine whether OSA was more common in those individuals with later-onset seizures or with worsening of seizure control, as compared to those with stable or improving epilepsy of earlier onset. We also examined these groups for variables related to OSA, such as scores on the Epworth Sleepiness Scale (ESS)⁵ and the Sleep Apnea section of the Sleep Disorder Questionnaire (SA-SDQ).⁶

METHODS Patients presenting to the Vanderbilt University epilepsy clinic from July 1, 2005, to April 30, 2006, who were 50 years of age or greater and who met study criteria were invited to participate in this study. To avoid selecting a biased

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sample, recruited participants were informed that the study would evaluate their sleep patterns, rather than test for OSA. Confirmation of the diagnosis of a single seizure or epilepsy was based on chart review and results of routine EEG, brain MRI, and video-EEG studies. Patients with all types of epilepsy, including generalized epilepsy, were included. Patients were excluded if they had provoked seizures (e.g., seizures induced by medications or metabolic abnormalities), associated neurologic disease (e.g., tumor, encephalitis, arteriovenous malformations), or unreliable seizure diagnosis. Patients were also excluded if they were unable to give informed consent for polysomnography, if they were medically unstable, requiring nursing care, or if they had a prior history of OSA, as many patients in the investigated age group were already being treated with continuous positive airway pressure (CPAP) or other therapies.

The participants were classified into two groups as follows, based on their seizure history. Grouping of these patients was done by an epilepsy specialist blinded to the sleep study results. Group 1: seizure onset at age 50 or older or seizure onset before age 50 with increased seizure frequency at or after age 50, defined by a 20% or greater increase in seizure frequency over the preceding 3 months. Group 2: seizure onset before age 50 with stable or improved seizure frequency at or after age 50.

Sleep histories and examinations were performed by the principal investigator and included previous diagnosis of sleep disorder, body mass index, and neck circumference. Medical records were utilized to obtain current antiepileptic medications, localization of seizures, and history of seizure frequency. Participants completed a survey prior to their sleep study which included the ESS, the SA-SDQ, and questions regarding seizure frequency and seizures occurring during sleep.

The participants stayed overnight at the Vanderbilt University General Clinical Research Center for one-night polysomnography (PSG) involving digital video, 16-channel EEG, submental EMG, electrooculography, snore microphone, airflow thermistor and nasal pressure transducer, thoracic and abdomen respiratory effort belts, pulse oximetry, electrocardiography, and anterior tibialis EMG (Nihon Kohden America, Foothill Ranch, CA). The recordings were done as close to the participants' habitual bedtimes as possible. A trained sleep technologist monitored the sleep study throughout the night and staged each study according to standard criteria.⁷ Apneas were scored if there was a $\geq 90\%$ decrement in airflow for ≥ 10 seconds and hypopneas were scored if there was a $\geq 50\%$ decrement in the nasal pressure transducer channel for ≥ 10 seconds with associated $\geq 3\%$ oxygen desaturation or ≥ 3 second EEG arousal.⁸ The average number of apneas and hypopneas per hour of sleep (apnea-hypopnea index [AHI]) was calculated. The PSGs were additionally reviewed by a sleep specialist (B.A.M.) blinded to the participant's epilepsy history to confirm the accuracy of the staging and respiratory scoring.

Medical records were reviewed and subjects were contacted by phone to determine the long-term outcomes of subjects diagnosed with OSA.

All statistical tests were performed using STATA statistical software (Statacorp, Release #9, College Station, TX, 2005). A p value of < 0.05 was considered significant. A Mann-Whitney nonparametric test was used to compare the AHI between the two groups. The continuous variables of age, neck circumference, body mass index, ESS score, and

SA-SDQ score were evaluated by independent samples two-tailed t test. Fisher exact tests were performed on categorical variables of gender and seizures occurring during sleep (either always or almost always during sleep vs never or sometimes during sleep). Spearman rank correlation was performed to evaluate the association between AHI and ESS score and between the AHI and SA-SDQ score.

RESULTS Of 290 patients presenting to the Vanderbilt Epilepsy Clinic aged 50 or older, 108 met inclusion criteria. Reasons for exclusion included nonepileptic spells (76), provoked seizures (29), previous diagnosis of OSA (29), associated neurologic disease (25), medical instability (20), and unreliable seizure history (3). Of the patients who met inclusion criteria, 17 declined participation because of difficulty obtaining transportation, 17 declined for other reasons, and 53 could not be reached. The characteristics of the group of patients who were eligible for the study but did not participate resembled the patients who did participate. Specifically, their mean age was 58.9 years (SD = 6.4) and 54% were male. Fifty-four percent (46 out of 85 individuals) would have been placed in Group 1 and 46% in Group 2. Twenty-one subjects consented to participate and constituted our reported sample. Their characteristics are summarized in table 1.

All participating subjects had recurrent seizures, even though one unprovoked seizure was sufficient for participation. Participants had the following epilepsy syndromes: partial epilepsy of temporal lobe (15) or frontal lobe (3) origin, idiopathic generalized (2), and unspecified (1). In Group 1, there were seven subjects who were having one or more seizures per month and four subjects who had late-onset seizures and were seizure-free at the time of study. All subjects in Group 2, except for one, were seizure-free.

Group 1 had a significantly higher AHI (figure), as well as higher ESS scores and SA-SDQ scores. The two groups were similar in age, body mass index, neck circumference, number of antiepileptic drugs currently used, and frequency of nocturnal seizures. Group 1 had more men. Overall, 52% of our sample had an AHI of 5 or greater (9 in Group 1 and 2 in Group 2), 33% had an AHI of 10 or greater (7 in Group 1 and none in Group 2), and 29% had an AHI of 15 or greater (6 in Group 1 and none in Group 2). There was a correlation between the overall ESS scores and AHI levels ($r = 0.578$, $p = 0.006$) and a trend in the correlation between the overall SA-SDQ scores and AHI levels ($r = 0.424$, $p = 0.055$).

Long-term outcomes for the subjects diagnosed with OSA are presented in table 2. All sub-

Table 1 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)

	Group 1, n = 11	Group 2, n = 10	p Value
Apnea-hypopnea index	23.2 (26.2)	3.1 (1.8)	0.002
SA-SDQ score	16.3 (4.1)	12.6 (3.7)	0.04
Epworth Sleepiness Scale score	11.6 (3.6)	5.9 (5.3)	0.009
Age, y	58.0 (9.7)	57.1 (7.0)	0.81
Men	82%	20%	0.003
Body mass index	27.6 (5.3)	26.6 (6.0)	0.67
Neck circumference, in	16.1 (1.5)	14.8 (1.8)	0.09
No. of antiepileptic drugs	1.5 (0.5)	1.8 (0.6)	0.32
Monotherapy	45.4%	30%	0.49
Nocturnal seizures predominantly	2	4	0.36

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

jects with AHIs of 5 or greater were offered CPAP, with three in Group 1 and one in Group 2 declining treatment. Of the six subjects in Group 1 who began treatment with CPAP, five were able to continue on CPAP, and three have noted improvements—one in both seizure control and excessive daytime sleepiness (No. 4), one in daytime alertness only (No. 5), and one in both seizure control and overnight sleep (No. 8). Subjects 4 and 8, who showed improved seizure control, both had a history of sleep-related (nocturnal) seizures. Compliance monitoring, available in Subject 8, showed that the subject used CPAP 98% of nights, for an average of 6 hours and 26 minutes

per night. Of note, this subject's AHI was only 5.3. One subject in Group 2 began treatment with CPAP and continues to use the device 10 months after titration, with improved daytime alertness.

DISCUSSION Our results indicate that the AHI, a measure of obstructive sleep apnea, was significantly higher in the group with later-onset seizures/worsening of seizures (Group 1) compared to the seizure-free/unchanged seizure frequency group (Group 2). The mean AHI of 23.2 for Group 1 is in the moderate range of OSA severity compared to mean AHI of 3.1 for Group 2 which is considered below the accepted cutoff for OSA (AHI of 5 or greater) by most sleep experts. The ESS and SA-SDQ scores were higher in Group 1 and were also correlated with elevated AHI.

Our study is unique in that it focuses on examining OSA in older adults with epilepsy. Older adults are most at risk for seizures and for OSA. Because new onset/worsening seizures were associated with an elevated AHI, this study suggests that OSA may be a contributing factor to worsening seizure control or new appearance of seizures in older adults. The cross-sectional nature of our study, however, does not allow us to determine if OSA facilitated seizures. Answering this question would require a prospective study design. Although our outcome data support that treatment of OSA improves seizure control, at least for sleep-related (nocturnal) seizures, these data are limited to only a few subjects, and require study in a large prospective trial with careful attention to monitoring of CPAP compliance. Our study is also limited in that we did not measure medication compliance, and it is conceivable that subjects in Group 1 had poorer compliance with

Figure Apnea-hypopnea index (AHI) for subjects in Groups 1 and 2

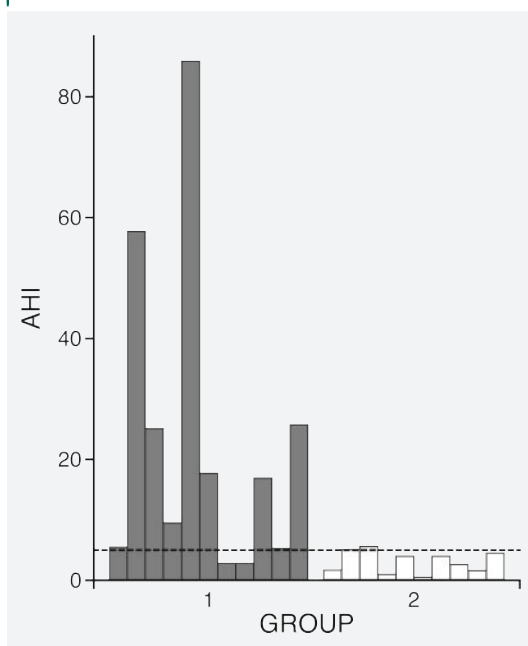


Table 2 Long-term outcomes in subjects diagnosed with OSA

Subject	Group, age (y), gender	AHI	Outcome
1	Group 1, 51, M	5.5	Declined treatment with CPAP. Seizures improved with optimization of AEDs.
2	Group 1, 70, M	57.7	Continuing to use CPAP 18 months after CPAP titration, although not fully adherent due to incomplete tolerance. No change in seizures or EDS.
3	Group 1, 55, M	25.1	Declined treatment with CPAP.
4	Group 1, 59, M	9.5	Continuing to use CPAP 9 months after titration, with improvement in seizures and EDS. Seizure type is predominantly sleep-related (nocturnal).
5	Group 1, 50, M	85.9	Continuing to use CPAP 1 year after titration, with improvement in EDS. Became seizure-free with initiation of oxcarbazepine.
6	Group 1, 55, M	17.7	Declined treatment with CPAP.
7	Group 1, 55, M	16.9	Continuing to use CPAP 9 months after titration, stating that he is only beginning to feel comfortable with CPAP. No change in seizures or EDS.
8	Group 1, 56, M	5.3	Continuing to use CPAP 8 months after titration, with improvement in seizures (all sleep-related-nocturnal) and nighttime sleep, but not daytime sleepiness, which she attributes to pregabalin. Documentation of excellent compliance.
9	Group 1, 50, M	25.7	Unable to tolerate CPAP.
10	Group 2, 58, M	5.1	Continuing to use CPAP 10 months after titration with improved alertness. Remains seizure-free (was seizure-free before starting CPAP).
11	Group 2, 66, F	5.6	Declined treatment with CPAP.

OSA = obstructive sleep apnea; AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure; AEDs = anti-epileptic drugs; EDS = excessive daytime sleepiness.

antiepileptic medications that those in Group 2. Of interest, the subjects in Group 2 were on average taking a higher number of antiepileptic drugs despite their better seizure control, although this difference was not significant. This is not surprising, as Group 1 included patients with later age at onset who were still trying AED monotherapy, while Group 2 included patients with early age at onset who eventually became seizure free with combination therapy.

Our work confirms that of prior investigations documenting a high prevalence of OSA in adults with epilepsy as compared to the general population. Approximately 9% of women and 24% of men in the general adult population (ages 30 to 60 years) had an AHI of 5 or greater⁹ while 20% of women and 28% of men in the general elderly adult population (greater than 65 years) had an AHI of 5 or greater.¹⁰ In our sample of adults with epilepsy aged 50 years and older, 30% of women and 73% of men had an AHI of 5 or greater. The reason for such a high prevalence of OSA in older adults with epilepsy is unclear and awaits further study. In our study, excessive seizure burden and use of multiple sedating antiepileptic drugs did not appear to be the cause as many subjects in our study were seizure-free and were taking only one antiepileptic drug. Our work also emphasizes that the ESS and the SA-SDQ are associated with OSA in the epilepsy population, confirming prior results.¹¹⁻¹³ These may be useful screening tools in this population.

Several retrospective reviews²⁻⁴ and one prospective study¹⁴ have documented improvement in seizure control with treatment of OSA in patients with epilepsy, although larger placebo-controlled trials will be necessary to definitely answer the question of whether treatment of OSA contributes to reduction of epileptic seizures. Treating OSA may also allow for better tolerability of antiepileptic medications in patients with daytime sleepiness, as daytime sleepiness is a major adverse effect reported by patients with epilepsy taking antiepileptic drugs.¹⁵ The established consequences of OSA include medical conditions such as hypertension, heart disease, cerebrovascular disease, and cognitive deficits.¹⁶⁻¹⁸ Patients with new-onset seizures in late adulthood commonly have ischemic stroke or hypertension¹⁹ and further exploration of the role of OSA in this group appears warranted.

Untreated sleep apnea is now considered an independent risk factor for stroke, and also worsens survival, length of hospitalization, and functional outcome after stroke.²⁰⁻²² In Parkinson disease, subjective daytime sleepiness has been associated with reported snoring and apnea, and sleep disordered breathing, along with dopaminergic treatments, may thereby contribute to decreased daytime alertness in this population.²³ In Alzheimer disease, sleep disordered breathing has been associated with decreased REM sleep,²⁴ and treatment of sleep disordered breathing with CPAP in this population reduces daytime sleepiness.²⁵

Taken together with these examples from the literature, our work provides further evidence that untreated OSA worsens neurologic disorders. Larger prospective studies appear warranted to confirm our findings and also to determine if treatment of OSA improves seizure control, daytime alertness, and other aspects of health-related quality of life in older adults with epilepsy.

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REFERENCES

- Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia* 1993;34:453–468.
- Devinsky O, Ehrenberg B, Barthlen GM, Abramson HS, Luciano D. Epilepsy and sleep apnea syndrome. *Neurology* 1994;44:2060–2064.
- Malow BA, Fromes GA, Aldrich MS. Usefulness of polysomnography in epilepsy patients. *Neurology* 1997;48:1389–1394.
- Vaughn BV, D’Cruz OF, Beach R, Messenheimer JA. Improvement of epileptic seizure control with treatment of obstructive sleep apnoea. *Seizure* 1996;5:73–78.
- Johns M. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991;14:540–545.
- Douglas AB, Bornstein R, Nino-Murcia G, et al. The Sleep Disorders Questionnaire. I: Creation and multivariate structure of SDQ. *Sleep* 1994;17:160–167.
- Rechtschaffen A, Kales A. *A Manual of Standardized Terminology, Techniques and Scoring Systems for Sleep Stages of Human Subjects*. Los Angeles: UCLA Brain Information Service/Brain Research Institute, 1968.
- American Sleep Disorders Association. EEG Arousals: Scoring rules and examples. A preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep* 1992;15:173–184.
- 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.
- Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Sleep-disordered breathing in community-dwelling elderly. *Sleep* 1991;14:486–495.
- Malow B, Bowes R, Lin X. Predictors of sleepiness in epilepsy patients. *Sleep* 1997;20:1105–1110.
- Manni R, Politini L, Sartori I, Ratti MT, Galimberti CA, Tartara A. Daytime sleepiness in epilepsy patients: evaluation by means of the Epworth sleepiness scale. *J Neurol* 2000;247:716–717.
- Weatherwax KJ, Lin X, Marzec ML, Malow BA. Obstructive sleep apnea in epilepsy patients: the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) is a useful screening instrument for obstructive sleep apnea in a disease-specific population. *Sleep Med* 2003;4:517–521.
- Malow BA, Weatherwax KJ, Chervin RD, et al. Identification and treatment of obstructive sleep apnea in adults and children with epilepsy: a prospective pilot study. *Sleep Medicine* 2003;4:509–515.
- Beghi E. Adverse reactions to antiepileptic drugs: a multi-center survey of clinical practice. *Epilepsia* 1986;27:323–330.
- Bassetti CL, Milanova M, Gugger M. Sleep-disordered breathing and acute ischemic stroke: diagnosis, risk factors, treatment, evolution, and long-term clinical outcome. *Stroke* 2006;37:967–972.
- Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;342:1378–1384.
- Parish JM, Somers VK. Obstructive sleep apnea and cardiovascular disease. *Mayo Clin Proc* 2004;79:1036–1046.
- Ramsay RE, Rowan AJ, Pryor FM. Special considerations in treating the elderly patient with epilepsy. *Neurology* 2004;62:S24–29.
- Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 2005;353:2034–2041.
- Parra O, Arboix A, Montserrat JM, Quinto L, Bechich S, Garcia-Eroles L. Sleep-related breathing disorders: impact on mortality of cerebrovascular disease. *Eur Respir J* 2004;24:267–272.
- Kaneko Y, Hajek VE, Zivanovic V, Raboud J, Bradley TD. Relationship of sleep apnea to functional capacity and length of hospitalization following stroke. *Sleep* 2003;26:293–297.
- Monaca C, Duhamel A, Jacquesson JM, et al. Vigilance troubles in Parkinson’s disease: a subjective and objective polysomnographic study. *Sleep Med* 2006;7:448–453.
- Cooke JR, Liu L, Natarajan L, et al. The effect of sleep-disordered breathing on stages of sleep in patients with Alzheimer’s disease. *Behav Sleep Med* 2006;4:219–227.
- Chong MS, Ayalon L, Marler M, et al. 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;54:777–781.

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