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Characteristics of refractory vs. medically controlled epilepsy patients with obstructive sleep apnea and their response to CPAP treatment

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ABSTRACT

Obstructive sleep apnea (OSA) commonly coexists with epilepsy, and treatment of OSA may decrease seizure frequency. However, it is unclear whether patients with medically refractory epilepsy have a higher incidence of OSA compared with well-controlled epilepsy patients and whether the two groups carry different risk factors.

Purpose: This study aimed to investigate the presence of OSA in patients with refractory vs. well-controlled epilepsy and their associated risk factors. We also assessed the benefits of treatment of OSA with continuous positive airway pressure (CPAP) in refractory epilepsy patients.

Methods: We retrospectively reviewed data from patients who presented to the Jacobs Neurological Institute Comprehensive Epilepsy Center of University at Buffalo from 2007 to 2010.

Results: There is a tendency for much higher incidence of OSA in our epilepsy population compared with the general population (15.2% vs. 4.41%). For patients with well-controlled epilepsy, older age, male gender, and higher seizure frequency were predictors of a diagnosis of OSA. However, in medically refractory epilepsy patients, diabetes and snoring predicted a diagnosis of OSA. Treatment of OSA with CPAP in refractory epilepsy patients improved their seizure control ($p < 0.02$).

Conclusion: This study confirms that OSA is common in epilepsy patients and treatment of OSA can improve seizure control in medically refractory cases. Patients with refractory epilepsy who have diabetes are more likely to have OSA.

1. Introduction

It is known that about 36% of epilepsy patients continue to have seizures despite antiepileptic drugs (AEDs).[1] Medically refractory epilepsy is a major cause of disability leading to considerable economic and social problems.[2,3] The most effective way of lowering the burden of epilepsy is by reducing the incidence of recurrent seizures. Therefore, recognizing and treating modifiable risk factors are of particular importance. It is well known that sleep deprivation can activate epileptic activity as depicted during electroencephalography (EEG) or occasionally cause seizures in subjects without pre-existing epilepsy.[4–9] Obstructive sleep apnea (OSA) is one of the most common sleep-breathing disorders which may exacerbate epilepsy by causing sleep disruption and deprivation, hypoxemia, and decreased cerebral blood flow.[10] Studies have shown epilepsy patients have higher incidence of OSA compared with the general population (10.2% vs. 4%).[11] In addition, in a previous study one third of epilepsy surgery candidates had OSA and they were more likely to have seizures during sleep than those without OSA.[12] Therefore, it is not surprising that OSA commonly coexists with epilepsy, and treatment of OSA may decrease seizure frequency.[13–16] Treatment with continuous positive airway pressure (CPAP) has been associated with improvement in seizure control.[2,17,18] However, there are conflicting data since Malow et al. showed no significant difference in seizure reduction in severely refractory epilepsy patients after CPAP treatment compared with the sham CPAP group.[19]

Higher incidence of OSA has been shown in males,[20] older population,[20,21] subjects with higher body mass index (BMI),[20] hypertension,[22] type 2 diabetes mellitus (DM),[23] and with Epworth Sleepiness Scale (ESS) score of 10 or greater.[24] A limited number of published studies have shown that epilepsy patients with OSA tend to be of male gender, older, heavier, and sleepier than "epilepsy only" patients.[11,12] However, it is unclear whether patients with refractory epilepsy have the same risk factors as patients with well-controlled epilepsy.

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The objective of this study was to compare characteristics of patients with medically refractory and well-controlled epilepsy as related to risk factors for sleep apnea including sex, age, obesity, hypertension, and DM and to determine the effects of CPAP treatment on seizure control in medically refractory vs. well controlled epilepsy population.

2. Materials and methods

We conducted a chart review retrospective study of the patients presenting to the Comprehensive Epilepsy Center of the Jacobs Neurological Institute, University at Buffalo from 2007 to 2010. The study was approved by Health Sciences IRB of the University at Buffalo. Exclusion criteria consisted of patients with seizures secondary to neoplasm, alcohol, or metabolic illness, poor compliance with antiepileptic drugs (AEDs), a history of drug abuse, vagus nerve stimulator (VNS), patients who were unaware of their seizures in the absence of reliable witness and finally patients who did not have follow-up for at least 6 months.

The diagnosis of epilepsy was made by an epileptologist based on clinical history of recurrent epileptic seizures and supporting EEG data. Seizure classification was confirmed by the same epileptologist based on prolonged video-EEG monitoring data and using International League Against Epilepsy (ILAE) criteria. Seizure frequency was determined by reviewing monthly seizure calendars which were filled by the patient or their caregivers. All patients had completed the same questionnaire which included Epworth Sleepiness Scale (ESS), seizure frequency, and comprehensive medical history. The presence of snoring and witnessed apneas was assessed by history.

Type and frequency of epileptic seizures, as well as previous and current antiepileptic drug (AED) treatment were reviewed. Medically refractory epilepsy was defined as any recurrent complex partial or generalized seizure in the past six months despite adequate use and compliance with at least two tolerated and appropriately chosen anticonvulsant medications in the past. Seizure freedom was defined as lack of recurrence of any complex partial or generalized seizure in the past six months. Improved seizure control was defined as reduction of seizure counts by at least 50% due to therapeutic intervention (AEDs, surgery, or CPAP) which is an established criteria used in epilepsy clinical trials.[25]

For the ease of statistical analysis and comparison of seizure frequencies between groups, we used modified Engel Criteria for seizure frequency and assigned a seizure frequency number between 0 to 12 for each patient visit.[26] As per modified Engel Criteria we assigned 0 for seizure free and off AEDs, 1 for seizure free and need for AEDs unknown, 2 for seizure free and requires AEDs to remain so, 3 for non-disabling simple partial seizures, 4 for non-disabling nocturnal seizures only, 5 for 1–3 seizures per year, 6 for 4–11 seizures per year, 7 for 1–3 seizures per month, 8 for 1–6 seizures per week, 9 for 1–3 seizures per day, 10 for 4–10 seizures per day, 11 for >10 seizures per day, and 12 for status epilepticus without barbiturate coma. By these criteria seizure frequency of 4 or above was assigned as medically refractory and seizure frequency of 3 or lower was considered as well-controlled.

Patients were routinely referred to have polysomnography (PSG) if there was clinical suspicion of OSA which included ESS > 12, snoring, or apneas during sleep observed by bed partner. Routine diagnostic overnight PSG was performed as previously described.[27] Briefly, sleep state was recorded with four channels of electro-encephalogram (C3/A2, C4/A1, O2/A1, O1/A2), two channels of electro-oculogram, and one-channel submental electromyogram. Breathing was assessed by monitoring chest and abdominal movements with piezopneumographs, and nasal and oral airflow using pressure transducers and thermistors. Arterial oxygen saturation was measured using a pulse oximeter. Respiratory events were scored as obstructive apnea when a decrease in the airflow was 90% or greater for 10 or more seconds, hypopnea when a decrease in the airflow was 50% or greater for 10 or more seconds, associated with either a 4% oxygen desaturation or an EEG arousal lasting 3 s or longer. The average number of apneas and hypopneas per hour of sleep (apnea-hypopnea index (AHI)) was calculated. OSA was rated according to the American Academy of Sleep Medicine standard guidelines: mild OSA with AHI of 5–15; moderate OSA with AHI of 16–30; severe OSA with AHI of more than 30.[28] CPAP treatment was initiated for patients with moderate or severe OSA, or mild OSA and excessive daytime sleepiness in accordance with official guidelines.[29] Compliance with CPAP treatment was assessed by data download from CPAP machine and/or clinical interview records.

2.1. Statistical analysis

In statistical regression modeling, the patient population was split into the medically refractory and medically controlled groups. We assessed the risk factors contributing to the incidence of sleep apnea in each of these groups. Wilcoxon signed rank test, student *t*-test, and Fisher exact test were used for categorical and continuous variables as appropriate.

Multiple logistic regression models were used to investigate the associations of predictor variables with OSA incidence adjusted for each possible predictor in the model. Significance was set at $p < 0.05$. Statistical analysis was performed using STATA (Statacorp, TX).

3. Results

Total of 312 charts were reviewed. We identified 197 subjects who met the inclusion criteria. Reasons for exclusion included seizures secondary to drug or alcohol abuse, neoplasm, metabolic causes ($n = 9$), non-compliance with AEDs ($n = 14$), VNS treatment ($n = 18$), loss to follow-up ($n = 25$), incomplete sleep/seizure questionnaire/history ($n = 47$), new-onset seizure with less than

Table 1
Characteristics of the patient population.

	Well-controlled	Refractory
Number	112	85
Age	44.8 ± 16.6	42.0 ± 15.1
Male	44 (39.3%)	34 (40.0%)
Age at seizure onset	27.6 ± 22.2**	18.8 ± 19.6**
BMI	27.0 ± 5.7*	29.2 ± 7.8*
Average number of AEDs	1.38 ± 0.62***	1.88 ± 0.85***
Monotherapy	78 (69.6%)***	31(36.5%)***
ESS	4.6 ± 3.5	5.8 ± 5.4
Snore	21 (18.8%)	21 (24.7%)
Difficulty falling sleep	20 (17.9)*	28 (32.9%)*
Difficulty staying sleep	33 (29.5%)	25 (29.4%)
Daytime sleepiness	16 (14.3%)	19 (22.4%)
Sleep disturbance	28 (25.0%)	34 (40.0%)*
Final seizure frequency	2.1 ± 0.7***	5.9 ± 1.6***
HTN	19 (17.0%)	15 (17.7%)
DM	6 (5.4%)	8 (9.4%)
CHF	13 (11.6%)	12 (14.1%)
CAD	7 (6.3%)	7 (8.2%)
Stroke	6 (5.4%)	11 (12.6%)
OSA	17 (15.2%)	13 (15.3%)

Values reported are means ± standard deviations, with corresponding percentages.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
BMI, body mass index; AED, antiepileptic drug; ESS, Epworth Sleepiness Scale; HTN, hypertension; DM, diabetes mellitus; CHF, congestive heart failure; CAD, coronary artery disease; OSA, obstructive sleep apnea.
Seizure frequency based on modified Engel Criteria.

Table 2
Characteristics of the patients with both epilepsy and OSA.

	Well-controlled, $N = 17$	Refractory, $N = 13$
Age (year)	54.9 ± 14.4	48.4 ± 9.9
Male	9 (52.9%)	6 (46.2%)
Age at seizure onset (year)	39.5 ± 21.1**	21.6 ± 15.0**
BMI (kg/m^2)	28.2 ± 5.6*	35.0 ± 10.3*
Number of AEDs	1.4 ± 0.61*	1.8 ± 0.55*
Monotherapy	12 (70.62%)*	3 (23.1%)*
ESS	5.1 ± 3.9	8.1 ± 5.7
Snore	5 (29.4%)†	9 (69.2%)†
Difficulty falling asleep	3 (17.6%)	5 (38.5%)
Difficulty staying asleep	10 (58.8%)	6 (46.2%)
Final Seizure frequency	2.0 ± 0.3***	5.5 ± 2.1***
Daytime sleepiness	6 (35.3%)	4 (30.8%)
HTN	6 (35.3%)	5 (38.4%)
DM	3 (17.7%)	4 (30.8%)
CHF	4 (23.5%)	2 (15.4%)
CAD	2 (11.8%)	2 (15.4%)
Stroke	2 (11.8%)	1 (7.7%)

Values reported are means ± standard deviations, with corresponding percentages.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
† $p = 0.06$.
Seizure frequency based on modified Engel Criteria.

six months on AEDs ($n = 1$), and death after single visit due to other reason ($n = 1$).

3.1. Characteristics of the patient population

Of the 197 subjects who met the inclusion criteria, 112 (56.9%) reached seizure freedom at the end of the study without surgical intervention, and 85 (43.1%) remained medically refractory. Seven patients who had medically refractory epilepsy underwent surgery for epilepsy and achieved seizure freedom as a result. The mean age was 43.6 ± 15.9 (range 19–88), and the age at the onset of first seizure was 23.7 ± 21.5 (range less than 1–77). The duration of follow up was 2.04 ± 1.28 years (range 0.66–5.11 years). The descriptive data for both groups are shown in Table 1.

There were no significant age or gender differences between medically refractory or well-controlled epilepsy patients. The incidence of hypertension, DM, depression/anxiety, congestive heart failure, coronary artery disease, stroke, or seizure types did not reach statistical significance between the two groups. As expected, patients with refractory epilepsy were taking more AEDs compared with those with well-controlled epilepsy (1.88 ± 0.85 vs. 1.38 ± 0.62 respectively, $p < 0.001$). In patients with either well-controlled or refractory epilepsy, there were no significant differences regarding the use of AEDs between subjects with OSA and without OSA, although more refractory patients were on benzodiazepines, phenytoin or topiramate ($p = 0.05$, 0.021, <0.0005 respectively) for their seizure control.

Patients with medically refractory seizures tended to have higher BMI, younger age of seizure onset, and more symptoms of sleep disturbance. There was no significant difference in OSA diagnosis between the refractory epilepsy and the seizure-free group.

3.2. Characteristics of patients with both epilepsy and OSA

Table 2 illustrates the demographic, clinical, and sleep related characteristics of those who have both epilepsy and OSA. Out of 197 subjects who were included in the study, 56 patients had ESS > 12 or snoring, 30 of which had confirmed OSA by PSG study. "epilepsy + OSA" patients were older than epilepsy patients without OSA (age 52.1 ± 12.9 vs. 42.1 ± 16.1, $p < 0.002$). Seventeen of them reached seizure freedom at the time of study before CPAP treatment, while 13 of them were considered having medically refractory epilepsy according to the criteria. The AHI and O_2 nadir between the two groups were not significantly different either (data not shown). "refractory epilepsy + OSA" patients had their first seizure at a younger age (21.6 ± 15.0 vs. 39.5 ± 21.1, $p < 0.01$), and were heavier (BMI 35.0 ± 10.3 vs. 28.2 ± 5.6, $p < 0.05$) than "medically controlled epilepsy + OSA" patients. Also they had more snoring and sleep disturbance symptoms but did not reach significance ($p = 0.06$) due to small sample size of patients.

Table 3
Regression model for patients with well-controlled epilepsy and OSA.

	Odd ratio	95% confidence interval		p-Value
Age	1.06	1.02	1.10	0.005
Male gender	5.12	1.20	21.81	0.027
Difficulty staying sleep	5.73	1.43	22.84	0.013
Daytime sleepiness	7.52	1.55	36.59	0.012
Initial seizure frequency	0.19	0.05	0.76	0.019

3.3. Factors associated with OSA

Multiple logistic regression models were conducted to adjust for the differences in age, gender, BMI, age at first seizure, hypertension, DM, cardiovascular disease, seizure frequency, ESS, difficulty falling sleep, difficulty staying sleep, daytime sleepiness, and snoring. For patients with well-controlled epilepsy (Table 3), it showed that older age, male gender, difficulty staying sleep, and daytime sleepiness were associated with higher chance for OSA diagnosis. Lower seizure frequency was associated with lower risk for OSA. However, in patients with refractory epilepsy, diabetes and snoring were the predictors of a diagnosis of OSA (Table 4).

3.4. Effect of CPAP treatment for seizure control

Of the 30 patients with both epilepsy and OSA, most suffered from complex partial seizures with or without secondary generalization (23 out of 30 or 77%). Fourteen were on at least two AEDs. Fifteen out of the 30 patients with "OSA + epilepsy" were compliant with CPAP treatment, 9 of which had well-controlled epilepsy and the other 6 suffered from refractory epilepsy. In CPAP compliant well-controlled epilepsy + OSA group, any additional benefit of CPAP for improving their seizure control could not be assessed. The remaining 6 patients with refractory epilepsy before CPAP treatment and OSA all showed significant improvement in seizures, with 3 patients reached seizure freedom at the end of study. In 4 out of these 6 patients the improvement in seizure frequency was solely due to the use of CPAP (1.31 ± 0.39 reduced to 0.15 ± 0.15 seizures per month, $p = 0.02$). In 2 patients other contributing factors to their seizure improvement were identified (i.e. epilepsy surgery and change in AED). Therefore, 100% of patients with coexisting refractory epilepsy and OSA, who were compliant with CPAP treatment, showed improved seizure control.

4. Discussion

Few previous studies have assessed the risk factors for OSA in an epilepsy population. They showed that these patients with

Table 4
Regression model for patients with refractory epilepsy and OSA.

	Odd ratio	95% confidence interval		p-Value
DM	9.39	1.44	61.2	0.02
Snoring	12.59	2.93	53.91	0.001

co-morbid epilepsy and OSA tend to be older, heavier, more frequently male, and sleepier than "epilepsy only" patients.[11,12] Our study is the first to compare different risk factors for OSA between well-controlled and refractory epilepsy groups. For patients with well-controlled epilepsy our study confirms the above mentioned findings that older age, male gender, and higher seizure frequency were predictors of a diagnosis of OSA. In refractory epilepsy patients with OSA, we found significantly higher BMI, snoring, sleep disturbance symptoms and younger age of seizure onset compared with patients with coexisting medically controlled epilepsy and OSA. In addition our patients with refractory epilepsy had more typical metabolic syndrome associated with sleep apnea including DM when adjusting for multiple variables. Therefore the presence of diabetes in refractory epilepsy subjects warrants further sleep study.

Our findings suggest a tendency for higher incidence of OSA compared with the study by Manni et al. (15.2% vs. 10.2%).[11] This difference may be due to different designs of the studies. The diagnostic method of portable PSG with no EEG recording might have underestimated the incidence of OSA in their patient population. Also, exclusion of epilepsy patients with DM and patients who were previously investigated for a sleep disorder could have contributed to their lower reported incidence of OSA in epilepsy patients.[11]

In this study we excluded the patients with vagus nerve stimulator due to known effects of VNS on sleep related breathing[30] and difficulties with CPAP titration in the presence of standard VNS on/off cycling mode.[31] It will be interesting to study the incidence of OSA in the subset of epilepsy patients with VNS.

Despite a recent proposal by the ad hoc Task Force of the ILAE Commission for definition of medically refractory epilepsy, there is still controversy as to the required length of seizure freedom to determine response to treatment. The task force defined drug resistant epilepsy as failure to respond to adequate trials of two tolerated and appropriately chosen AED schedules to achieve sustained seizure freedom. The length of time required to determine responsiveness to treatment was defined as seizure-free for three times pretreatment interseizure interval, or 12 months, whichever is longer.[32]

In the study by Malow et al.[12] which studied sleep disorder in medically refractory epilepsy patients, the patients had at least one seizure in the last month and there were 33% of subjects found to have OSA. We chose to use more clinically relevant criteria for refractory epilepsy, which was any recurrent complex partial or generalized seizure in the past six months despite adequate use of at least two tolerated and appropriately chosen anticonvulsant medications in the past.

Sleep can influence seizures and interictal epileptiform discharges. It has been shown that during non-rapid eye movement (NREM) sleep seizure activity can be more common due to neuronal synchronization and recruitment of a critical mass of neurons to initiate and sustain a seizure.[33] One example is the syndrome of continuous spike-wave activity during slow-wave sleep which is inhibited during wakefulness and REM sleep.[34,35] Desynchronization during REM sleep may restrict the field of the above discharges.[35,36] Others have shown that patients with epilepsy are at higher risk for apnea than the general population, due to sedentary lifestyle or the effects of antiepileptic therapies on OSA.[12] Sleep fragmentation in OSA which results in increased sleep stage transitions can facilitate the occurrence of seizures,[14,37] whereas epileptic seizures can induce apneas.[38] Seizures and interictal epileptiform spikes are facilitated by lighter stages of sleep and during sleep–wake transition.[39] There is report of direct effect of CPAP on reducing the interictal spikes and therefore potential for reducing epileptogenicity.[40]

There have been several studies that showed improvement of epileptic seizures with treatment of OSA.[2,14,15,17,41,42] In these studies about 40–56% of patients showed improvement in seizure frequencies independent of their AED changes. Vendrame et al.[17] in a retrospective study showed 28 patients out of 41 subjects with OSA and epilepsy were CPAP compliant. Sixteen (57%) of CPAP compliant patients became seizure free compared with 3 of non-compliant patients. However, Malow et al. in a randomized pilot trial[19] showed no significant difference in seizure frequency reduction in CPAP vs. sham CPAP treated groups. Only 4 out of their 28 epilepsy subjects treated with CPAP became seizure free. The population of epilepsy patients in their study was severely refractory (average baseline seizure frequency of 14.7–16.1 month^{-1}). The hypoxic effects in this severely refractory epilepsy population might have been too advanced to be reversed by CPAP therapy. Also, the patients were only followed for eight weeks after the initiation of CPAP treatment, which may be too short to see any effects from the treatment. We have found that all of our patients with refractory epilepsy and OSA who were compliant with CPAP showed significant improvement in their seizure control. Although our sample size was small, the results warrant emphasizing CPAP compliance in medically refractory epilepsy patients with coexisting OSA as an adjunctive non-pharmacological means to help their seizure control.

One of the strengths of our study is the fact that we studied all patients who were referred to the adult epilepsy center regardless of their sleep problems. The epilepsy population we studied was not biased toward any sleep-related problems. Also, to our knowledge there are no other studies comparing the characteristics and risk factors in refractory vs. well controlled epilepsy population who have coexisting OSA.

The limitations of our study include that the patient population is from a tertiary epilepsy center which may include more patients with medically refractory epilepsy. Also, by retrospective nature of this study, not all of the enrolled patients received PSG evaluation. This may have underestimated the incidence of OSA in our epilepsy population. In addition due to retrospective study, other possible confounding factors such as non-compliance with AED use and inaccurate seizure count cannot be ruled out. Other limitation was small sample size in CPAP compliant epilepsy + OSA patients.

We need to better identify epilepsy patients who are at higher risk for OSA since treating OSA with CPAP can improve seizure control and quality of life. Further prospective studies are needed to investigate predictors of OSA in an epilepsy population and to determine the importance of diagnosis and treating OSA in management of patients with medically refractory epilepsy. This will give a whole new perspective in treatment of epileptic seizures before resorting to polypharmacy and invasive surgery.

5. Conclusions

Our findings support previous studies that show a higher percentage (15.2%) of OSA in epilepsy patients compared to the general population (2% for women and 4% for men).[43] However, we did not find higher OSA rate in refractory vs. well-controlled epilepsy patients. The use of CPAP in our refractory epilepsy patients with OSA significantly improved their seizure control. Patients with refractory epilepsy who have diabetes are more likely to have OSA. We suggest that in refractory epilepsy patients with diabetes specific attention should be focused on further sleep study tests.

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