Obstructive sleep apnea is common in medically refractory epilepsy patients
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Article abstract—Background: Previous reports have documented the coexistence of obstructive sleep apnea (OSA) and epilepsy and the therapeutic effects of treatment on seizure frequency and daytime sleepiness. The authors’ objective was to determine the prevalence of OSA and its association with survey items in a group of patients with medically refractory epilepsy undergoing polysomnography (PSG). Methods: Thirty-nine candidates for epilepsy surgery without a history of OSA underwent PSG as part of a research protocol examining the relationship of interictal epileptiform discharges to sleep state. Subjects also completed questionnaires about their sleep, including validated measures of sleep-related breathing disorders (Sleep Apnea Scale of the Sleep Disorders Questionnaire [SA/SDQ]) and subjective daytime sleepiness (Epworth Sleepiness Scale [ESS]). Results: One-third of subjects had OSA, defined by a respiratory disturbance index (RDI) ≥ 5. Five subjects (13%) had moderate to severe OSA (RDI > 20). Subjects with OSA were more likely to be older, male, have a higher SA/SDQ score, and more likely to have seizures during sleep than those without OSA (p < 0.05). Seizure frequency per month, the number or type of antiepileptic drugs (AED) prescribed, the localization of seizures (temporal versus extratemporal), and the ESS were not statistically different between the two groups. Conclusions: In our sample, previously undiagnosed obstructive sleep apnea was common, especially among men, older subjects, and those with seizures during sleep. The impact of treating OSA on seizure frequency and daytime sleepiness in medically refractory epilepsy patients warrants further controlled study.

NEUROLOGY 2000;55:1002–1007

Sleep disorders and epilepsy are common, treatable conditions. Unrecognized sleep-disordered breathing has been estimated to affect up to 24% of men and 9% of women, with multiple case series documenting its coexistence with epilepsy. These reports have also documented an improvement in seizure control, daytime sleepiness, or both when obstructive sleep apnea (OSA) is treated. These therapeutic benefits are particularly relevant in patients whose seizures persist despite treatment with antiepileptic drugs.
drugs (AED) or who require sedating doses of AED to achieve seizure control. The prevalence of OSA in such patients with medically refractory epilepsy, however, has not been established. In addition, the clinical features associated with OSA in this population are not well characterized.

We report a high prevalence of OSA among a group of medically refractory epilepsy patients undergoing polysomnography (PSG). These subjects were participating in a sleep protocol examining the relationship of interictal epileptiform discharges (IED) to sleep state. The first night of PSG used to screen for sleep disorders, including sleep apnea; the second night of PSG was used to determine the relationship of IED to sleep. Subjects were selected for study because they were candidates for epilepsy surgery, rather than because of sleep-related complaints. As part of the protocol, subjects also completed questionnaires about their nighttime sleep, sleep-related breathing, and daytime sleepiness. This enabled us to assess the usefulness of survey responses in combination with clinical characteristics for predicting those at risk for sleep-disordered breathing.

Methods. Subjects. All subjects undergoing presurgical evaluation in the University of Michigan Epilepsy Laboratory between December 1995 and February 1997 and who met study criteria were asked to participate in the sleep protocol. Fifty-two percent agreed, for a subsample of 26 subjects. The most common reasons for not participating were being unable to miss work or arrange for childcare or transportation. An additional 13 subjects undergoing presurgical evaluations and meeting study criteria were recruited before December 1995 (as part of a pilot study on the effects of sleep on IED) or after February 1997 (as part of a follow-up study on the effects of sleep on IED in extra-temporal epilepsy). Some of these IED data have been previously reported.6,7 Participants met the following criteria: aged 18 to 65 years; ability to give informed consent; a history of recurrent unprovoked complex partial seizures, with at least one seizure in the last month; ictal semiology and long-term monitoring (LTM) consistent with complex partial seizures; no history of psychogenic seizures; no prior epilepsy surgery; and no recent medication discontinuation. Subjects were on constant doses of AED for at least 2 weeks before study. No subjects had been previously diagnosed with OSA. The primary goal of the two-night sleep research protocol was to assess the relationship between IED and sleep state. Comprehensive PSG was performed on the first night of study to obtain information about the subjects’ sleep quality and to detect any unrecognized sleep disorders that might confound the results of the IED analysis. The protocol was approved by the University of Michigan Institutional Review Board.

PSG. PSG was performed in all 39 subjects in the University of Michigan General Clinical Research Center. Overnight recordings were performed on 21-channel polygraphs or 32-channel computerized EEG systems (Grass–Telefactor Corp., West Conshohocken, PA) and EEG, electro-oculogram, submental EMG, nasal–oral airflow, respiratory effort, pulse oximetry, and anterior tibialis EMG were recorded. In our laboratory, an apnea is defined by a decrease in airflow or effort to 20% or less of baseline for 10 or more seconds. A hypopnea is defined by any decrease in airflow or effort for 10 or more seconds that is accompanied by either EEG signs of arousal (defined by the American Academy of Sleep Medicine criteria)8 or a 4% or greater decrease in oxygen saturation. The respiratory disturbance index (RDI) is calculated by dividing the number of apneas and hypopneas by the total number of hours asleep. OSA was defined by an RDI ≥ 5.9 Studies were scored by trained PSG technologists and reviewed by the first author (BAM).

Questionnaire data and medical record review. Questionnaire data included: 1) The Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA/SDQ),10 a validated measure of sleep apnea (see Appendix); 2) The Epworth Sleepiness Scale (ESS), a validated measure of subjective daytime sleepiness which assesses the likelihood of a subject to fall asleep in certain situations, such as watching television;11 3) Information on seizure frequency, and whether seizures occurred during sleep. Those reporting seizures during sleep either part of the time or most of the time (as opposed to rarely or never) were classified as having seizures during sleep. The SA/SDQ is a 12-item survey with total scores ranging from 0 to 60. Using receiver-operating characteristic curves, cutoff points for apnea of 36 for men and 32 for women have been suggested, although these cutoffs await confirmation in larger scale studies.10 The ESS is an eight-item scale with total scores ranging from 0 to 24, with an ESS score greater than 10 generally regarded as consistent with excessive daytime sleepiness.11

A proportion of subjects completed the protocol before we began giving the SDQ and ESS routinely. Therefore, SA/SDQ scores were available for 28 subjects, ESS scores were available for 34 subjects, a history of loud snoring or witnessed apnea was available for 36 subjects, and body mass index (BMI; weight in kilograms/height in meters squared) was available for 37 subjects. Information regarding seizure frequency and seizures during sleep was available for all subjects. Medical records were reviewed to obtain information regarding the number and type of antiepileptic drugs (AED), other medications, type of seizure (complex partial, secondarily generalized, or both), localization of the epileptogenic region (temporal versus extratemporal; based primarily on LTM results and also on brain imaging), whether treatment was prescribed for OSA, and follow-up in those who were treated. Levels of AED were available in the majority of subjects (29 out of 39) for phenytoin, carbamazepine, valproate, myclobutin, and phenobarbital, but not for lamotrigine or gabapentin. Therapeutic ranges were 10 to 20 mg/L for phenytoin, 4 to 12 mg/L for carbamazepine, 40 to 100 mg/L for valproate, 4 to 12 mg/L for myclobutin, and 15 to 40 mg/L for phenobarbital.

Statistical analysis. For all statistical tests, the level of significance was set at α = 0.05. All statistical tests were performed using the SPSS statistical analysis package (SPSS Inc, Chicago, IL). Major predictor variables between subjects with OSA and those without were compared using two-tailed independent sample t-tests for continuous data, and χ² or Fisher’s Exact tests for categorical data. Continuous variables included age, seizures per month, the number of AED, the total SA/SDQ score, BMI, October (1 of 2) 2000 NEUROLOGY 55 1003
and ESS score. Categorical variables included gender; AED type (presence or absence of phenytoin, carbamazepine, valproate, lamotrigine, or gabapentin); presence of secondarily generalized tonic-clonic seizures; presence of additional medication having sedating effects or effects on upper airway tone; localization of the epileptogenic region (temporal versus extratemporal); a history of seizures occurring habitually during sleep either part of the time or most of the time (as opposed to rarely or never); and self-reported loud snoring or witnessed apneas occurring occasionally, often, or almost always (combined into one response as subjects rarely reported being told that they had apnea). Seizures per month were also grouped into those with 10 or more seizures per month and those with fewer than 10 seizures per month. Predictor variables were also compared within logistic regression models.

**Results.** Univariate and bivariate analyses. Thirteen (33%) of 39 subjects had respiratory disturbance indexes (RDI; apneas and hypopneas per hour of sleep); mO$_2$ = minimum oxygen saturation; PHT = phenytoin; PRM = primidone; GBN = gabapentin; CPAP = continuous positive airway pressure; CBZ = carbamazepine; VPA = valproic acid; LTG = lamotrigine; TPM = topiramate.

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Age, y/sex</th>
<th>RDI</th>
<th>mO$_2$</th>
<th>Antiepileptic drugs</th>
<th>Treatment of OSA</th>
<th>Treatment outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40/M</td>
<td>61.2</td>
<td>83</td>
<td>PHT, PRM, GBN</td>
<td>Yes, after surgery</td>
<td>Improvement in daytime alertness with CPAP but poor compliance after 1 y</td>
</tr>
<tr>
<td>2</td>
<td>46/M</td>
<td>32.2</td>
<td>87</td>
<td>CBZ</td>
<td>Yes, after surgery</td>
<td>Did not tolerate CPAP</td>
</tr>
<tr>
<td>3</td>
<td>30/M</td>
<td>23.6</td>
<td>90</td>
<td>PHT</td>
<td>Yes, after surgery</td>
<td>Tolerating oral appliance well with improved daytime alertness</td>
</tr>
<tr>
<td>4</td>
<td>35/M</td>
<td>23.0</td>
<td>84</td>
<td>PHT, VPA</td>
<td>Yes, after surgery</td>
<td>Improvement in daytime alertness with CPAP but poor compliance after 1 y</td>
</tr>
<tr>
<td>5</td>
<td>24/M</td>
<td>20.5</td>
<td>87</td>
<td>PHT, VPA</td>
<td>Yes, before surgery</td>
<td>Did not tolerate CPAP</td>
</tr>
<tr>
<td>6</td>
<td>45/M</td>
<td>5.0*</td>
<td>87</td>
<td>PHT, LTG</td>
<td>Yes, after surgery</td>
<td>Improved CPAP use after retitration and nasal pillows added; improved daytime alertness</td>
</tr>
<tr>
<td>7</td>
<td>54/F</td>
<td>8.9</td>
<td>91</td>
<td>PHT, LTG</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>46/M</td>
<td>8.3</td>
<td>90</td>
<td>VPA, LTG</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>43/M</td>
<td>8.0</td>
<td>79</td>
<td>CBZ, GBN</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>48/F</td>
<td>7.4</td>
<td>89</td>
<td>PHT</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>39/F</td>
<td>6.7</td>
<td>88</td>
<td>CBZ, LTG</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>44/F</td>
<td>6.0</td>
<td>89</td>
<td>VPA, LTG</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>24/M</td>
<td>5.7</td>
<td>90</td>
<td>CBZ</td>
<td>No</td>
<td>—</td>
</tr>
</tbody>
</table>

* Repeat RDI 1 year later was 31.7.

RDI = respiratory disturbance index (number of apneas and hypopneas per hour of sleep); mO$_2$ = minimum oxygen saturation; PHT = phenytoin; PRM = primidone; GBN = gabapentin; CPAP = continuous positive airway pressure; CBZ = carbamazepine; VPA = valproic acid; LTG = lamotrigine; TPM = topiramate.

and a higher proportion were men. A higher proportion reported seizures during sleep. The total SDQ score and specific subitems within this scale, including BMI and loud snoring or witnessed apneas, were higher or more frequent in the OSA group. Localization of the epileptogenic region (temporal versus extratemporal) and seizure frequency per month (analyzed both as a continuous variable and as a categorical variable of 10 or greater seizures per month versus fewer than 10 seizures per month) did not differ significantly between the groups.

The number or type of AED prescribed did not differ significantly between the groups. In five subjects, all on phenytoin, levels were above the therapeutic range but still within the range used to treat refractory seizures (26 to 29.3 mg/L). Two of these five subjects had OSA. Fourteen subjects were taking additional medications, which included antidepressants (eight subjects), antihypertensive or cardiac agents (five subjects), asthma inhalers (two subjects), histamine receptor blockers for gastroesophageal reflux (one subject), antipsychotic medication (one subject), and hormone replacement therapy (three subjects; e.g., thyroid, estrogen, and progesterone). Groups did not differ in the number of subjects taking antidepressants, which may have sedating effects and also improve upper airway tone and reduce REM sleep.

The ESS scores did not differ significantly between the groups. Subjects reporting seizures during sleep had a higher total SDQ score than those not reporting seizures during sleep (26 ± 6.8 versus 20.2 ± 5.1; mean ± SD; $p = 0.02$). However, BMI was not different between the subjects reporting seizures during sleep (26.9 ± 5.9) and those not reporting seizures during sleep (23.8 ± 4.5; $p = 0.09$).
Table 2 Differences between subjects with and without obstructive sleep apnea (OSA)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OSA, n = 13</th>
<th>No OSA, n = 26</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA/SDQ score, mean ± SD</td>
<td>28.9 ± 7.2</td>
<td>21.3 ± 5.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Loud snoring or witnessed apnea, n (%)</td>
<td>8 (62)</td>
<td>6 (23)</td>
<td>0.01</td>
</tr>
<tr>
<td>Body mass index, mean ± SD</td>
<td>28.6 ± 7.1</td>
<td>24.3 ± 4.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>39.9 ± 9.2</td>
<td>32.9 ± 9.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>9 (69)</td>
<td>9 (35)</td>
<td>0.04</td>
</tr>
<tr>
<td>Seizures during sleep, n (%)</td>
<td>10 (77)</td>
<td>11 (42)</td>
<td>0.04</td>
</tr>
<tr>
<td>Temporal localization, n (%)</td>
<td>11 (85)</td>
<td>25 (81)</td>
<td>0.76</td>
</tr>
<tr>
<td>Seizures/mo, n, mean ± SD</td>
<td>12.1 ± 15.0</td>
<td>10.8 ± 12.1</td>
<td>0.77</td>
</tr>
<tr>
<td>Antiepileptic drugs, n, mean ± SD</td>
<td>1.69 ± 0.6</td>
<td>1.50 ± 0.6</td>
<td>0.60</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score, mean ± SD</td>
<td>7.3 ± 3.6</td>
<td>6.0 ± 3.6</td>
<td>0.33</td>
</tr>
<tr>
<td>Secondarily GTCS, n (%)</td>
<td>5 (38)</td>
<td>8 (31)</td>
<td>0.63</td>
</tr>
<tr>
<td>Subjects taking antidepressant medications, n (%)</td>
<td>3 (23)</td>
<td>5 (19)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

* Defined as occasionally, often, or almost always.

Our results indicate that OSA is common among subjects with medically refractory seizures. One-third of subjects had an RDI ≥ 5, indicating mild OSA, and 13% of subjects had an RDI > 20, indicating moderate to severe OSA. In addition, we found that OSA was associated with increasing age, male gender, seizures during sleep, and SA/SDQ score, but not with seizure frequency or type, AED number or type, antidepressant use, seizure localization, or ESS score. The prevalence of OSA in our subjects was higher than that reported in a population-based study of adult state workers without epilepsy, in which 24% of men and 9% of women had an RDI ≥ 5.1 In our sample, 50% of men and 19% of women had an RDI ≥ 5.

Our study is unique in that we performed PSG as part of a research protocol in a group of medically refractory epilepsy patients who were not previously diagnosed with OSA. Our subjects underwent PSG as part of an unrelated study examining the relationship of IED to sleep. In a retrospective review of epilepsy patients undergoing PSG in our laboratory, OSA was present in 45 (71%).3 However, these patients had been referred specifically for the evaluation of sleep disorders, including OSA.

Our results support the use of screening questions and questionnaires related to sleep-disordered breathing in assessing epilepsy patients for OSA. Although most subjects did not report having been told that they stopped breathing during sleep, many reported that they had been told they snored loudly. Loud snoring and an increased BMI were associated with OSA; OSA was also higher in men. The strongest predictor of OSA was the SA/SDQ, a self-administered screening questionnaire that incorporates self-reported loud snoring or witnessed apnea, BMI, smoking, a history of hypertension, and other factors (see Ap-
had an RDI
workers in Wisconsin, 9% of women and 24% of men
study of sleep-disordered breathing in adult state
possibilities for this lack of sensitivity. First, not all
increased risk of sleep-disordered breathing.
An increase in one SD in any measure of body
likely than women to have sleep-disordered breath-

In contrast to the SDQ, the ESS, a measure of
subjective daytime sleepiness, did not differ among
subjects with and without OSA. There are several
possibilities for this lack of sensitivity. First, not all
subjects with OSA have daytime sleepiness. In the
study of sleep-disordered breathing in adult state
workers in Wisconsin, 9% of women and 24% of men
had an RDI ≥ 5. However, only 2% of women and 4%
men had OSA syndrome, defined as an RDI ≥ 5
and daytime hypersomnolence.1 Second, subjects
with epilepsy may be sleepy for other reasons be-
side OSA, including AED effects, seizures, or the
effects of seizures on sleep.13,14 Finally, subjects may
underestimate their degree of daytime sleepiness or
may change their lifestyle to compensate over time
for decreased alertness.9

The reasons why the prevalence rate of OSA was
so high in our sample as compared with non–epi-
lepsy patient populations are uncertain. One possi-
bility is that AED influence OSA. Barbital, benzodiazepines, and weight gain in patients treated
with valproate, may precipitate or exacerbate
OSA.15,16 Although no association was found between
OSA and AED number or type, our subjects were
taking a variety of medication combinations, and the
number taking any given AED was relatively small.
Only one of three subjects on sedative AED (pheno-
barbital, myoline, or clonazepam) had OSA. Two of
five subjects with supertherapeutic AED levels had
OSA. Larger studies will be necessary to determine
whether specific AED regimens exacerbate OSA,
whether supertherapeutic AED levels influence OSA,
and whether patients with medically refractory sei-
zures have a higher prevalence of OSA than those with
controlled seizures, or those without epileptic seizures.

The association of OSA with seizures during sleep
in our series is intriguing. We previously reported in
abstract form that subjects with seizures during sleep were more likely to have OSA as compared
with those with seizures during wakefulness.17 How-
ever, we cannot determine from our data whether
subjects reporting seizures during sleep were more
likely to have OSA for other reasons, such as a
higher prevalence of obesity, or whether OSA was
causal in facilitating seizures during sleep. Subjects
reporting seizures during sleep showed a trend to-
ward a higher BMI, but this was not statistically
significant. Alternatively, several case series have
documented an improvement in seizure control with
treatment of OSA, implying that OSA may facilitate
seizures.2-5 A variety of seizure-provoking mech-
anisms have been proposed. Cerebral hypoxemia, de-
creased cardiac output, and cardiac arrhythmias
seem unlikely, given that we have not encountered
any examples of epileptic seizures resulting from
acute cardiopulmonary changes in our sleep labora-
tory population in the last 15 years.8 Other proposed
mechanisms include sleep deprivation and fragment-
tion of sleep with frequent stage shifts, arousals,
and entries into sleep after arousal. If sleep depriva-
tion is the assumed mechanism, one might expect
that seizures during both sleep and wakefulness
would be facilitated in patients with epilepsy with
OSA. In contrast, if sleep fragmentation and fre-
quent stage shifts resulting from apneas are respon-
sible for provoking seizures, then seizures during
sleep may be facilitated preferentially in patients
with epilepsy with OSA. These proposed mecha-
nisms await further experimental investigation.

Poor compliance with CPAP, the first-line treat-
ment for OSA, is a commonly recognized problem
that is not unique to our subjects.19 Many patients
find it cumbersome to use CPAP equipment nightly.
In one study, simple interventions were found to im-
prove CPAP compliance.19 These interventions in-
clude providing written educational materials and
contact with patients in the first few weeks after
treatment is initiated to troubleshoot problems and
encourage use. A variety of surgical techniques are avail-
able for those with OSA who are not able to tolerate
CPAP, although the success rate of surgery is not as
high as with CPAP. Nonsurgical alternatives to CPAP
treatment for mild to moderate OSA include weight
loss, positional therapy to avoid the supine position,
avoidance of alcohol, and oral appliances.9

We cannot comment on the effects of OSA treat-
ment on seizure control and daytime sleepiness in
our sample because only a few subjects were treated.
Although case series have suggested that treating
OSA is beneficial for seizure control and for improve-
ment of daytime sleepiness, randomized clinical tri-
als will be necessary to definitively answer this
question and to identify those patients in whom sei-
zures will respond to treatment. A relevant question
is whether subjects with mild OSA (RDI between 5
and 20), as compared with those with more severe
OSA, may benefit from treatment. If seizures, daytime
sleepiness, or both respond to treatment of even mild
OSA, it may be worth the effort and expense necessary
to diagnose and treat all patients with epilepsy pre-
senting with symptoms of sleep-disordered breathing.
Further investigations of sleep-disordered breathing
in patients with epilepsy may also enhance our un-
derstanding of the mechanisms whereby sleep disor-
ders, and their treatment, affect seizure control.
Appendix

Sleep Apnea Scale of the Sleep Disorders Questionnaire

1. I am told I snore loudly and bother others.
2. I am told I stop breathing (“hold my breath”) in sleep.
3. I awake suddenly gasping for breath, unable to breathe.
4. I sweat a great deal at night.
5. I have high blood pressure (or once had it).
6. I have a problem with my nose blocking up when I am trying to sleep (allergies, infections).
7. My snoring or my breathing problem is much worse if I sleep on my back.
8. My snoring or breathing problem is much worse if I fall asleep right after drinking alcohol.
9. What is your current weight? (Five categories)
10. How many years were you a smoker? (Five categories)
11. How old are you now? (Five categories)
12. Body mass index (calculated from weight in kilograms/height in meters squared) (Five categories)

References