Seizure 1996; **5**: 73–78

Improvement of epileptic seizure control with treatment of obstructive sleep apnoea

BRADLEY V. VAUGHN, O'NEILL F. D'CRUZ, ROBERT BEACH & JOHN A. MESSENHEIMER

Department of Neurology, School of Medicine, University of North Carolina at Chapel Hill, NC, USA

Address for correspondence: Dr. Bradley V. Vaughn, Dept. of Neurology C.B.#7025, University of North Carolina, Chapel Hill, N.C. 27599-7025, USA

Sleep deprivation increases the risk of recurrent seizures in epileptic patients. We identified 10 patients with recurrent seizures and sleep disruption related to obstructive sleep apnoea. Two patients were treated with positional therapy and the remaining eight patients were treated with continuous positive airway pressure. Three of the patients became seizure free and a fourth patient had a greater than 95% reduction in seizure frequency following only the initiation of therapy for the sleep apnoea. Three of these four patients responding to therapy, had a state-dependent seizure pattern. Two of the four responders did not exhibit the typical body habitus for obstructive steep apnoea. Three additional patients improved in seizure frequency with change in anticonvulsant medication and treatment of the obstructive sleep apnoea. The remaining three patients had less than 50% reduction in seizure frequency with treatment of the obstructive sleep apnoea. These results indicate sleep disruption caused by sleep apnoea may increase the seizure frequency in some epileptic patients. Regardless of body habitus, epilepsy patients should be questioned carefully for a history of sleep disturbance and state dependence to their seizures. Treatment of sleep disorders in this population may lower the frequency of recurrent seizures.

Key words: epilepsy; obstructive sleep apnoea; sleep deprivation; CPAP.

INTRODUCTION

Sleep has long been known to affect epilepsy. In 1881, Gower studied the relationship of sleep/awake state to epilepsy, noting that 21% of patients had seizures solely during sleep[1]. He noted that other patients had seizures only during the awake state (42%) while a third group had seizures during both the awake and asleep states (37%). Later investigation, by Janz, revealed that some individuals have seizures primarily in the first two hours after awakening. Janz coined the term 'awakening' epilepsies for these individuals, and referred to seizures occurring without dependence on the sleep/awake state as diffuse epilepsies[2,3]. The sleep-related epilepsies and the awakening epilepsies can be grouped into state-dependent epilepsies and the diffuse epilepsies as a state independent epilepsies.

Sleep deprivation may exacerbate seizures in some patients with epilepsy[4–7]. Sleep deprivation is frequently used in long-term epilepsy monitoring settings to promote seizures, and may also uncover interictal abnormalities on electroencephalographic (EEG) recordings[4]. This activation of interictal activity may be related to the promotion of the onset of sleep[8], but this point has yet to be resolved. Sleep may activate interictal activity in approximately one third of epileptic patients and up to 90% of subjects with sleep–wake related, or state dependent, epilepsies[5,9–11].

Obstructive sleep apnoea (OSA) disrupts sleep and can cause severe sleep deprivation. In one population study, as high as 6% of males between 35 and 65 years old had OSA at night[12]. Neurological manifestations of OSA include cognitive decline and autonomic symptoms. However, seizures as a direct result of apnoea are rare. In one patient, an apnoea in sleep reportedly cause a seizure after severe oxygen desaturation and cardiac arrest[13]. In another patient who had epilepsy, Wyler reported some improvement in seizure intensity with treatment of sleep apnoea[14]. Since our initial

This paper was previously presented in part at the American Epilepsy Society Meeting in December of 1993.

1059-1311/96/010073 + 06 $12.00/0

presentation a subsequent report of treatment of sleep apnoea on epilepsy demonstrated similar results[15,16]. Considering these factors, we reviewed our patient population for patients with both OSA and epilepsy to examine the effect of treatment of OSA on seizure frequency.

METHODS

We sequentially identified 10 adult epileptic subjects with OSA who were seen in the University of North Carolina Epilepsy Clinic between January 1991 and April 1993. The diagnosis of epilepsy and seizure type was determined by an epileptologist, on the basis of historical and laboratory data. Seizure frequency on pretreatment regimen was determined by history and seizure calendars prior to the start of therapy for sleep apnoea.

The diagnosis of OSA was determined on the basis of clinical history and overnight polysomnograms. Overnight polysomnograms were performed recording electro-oculogram, EEG, submental electromyogram, surface electromyogram from left and right anterior tibialis, electrocardiogram (ECG), nasal/oral air temperature, continuous carbon dioxide monitoring from the nose, chest movement, abdominal movement and oxygen saturation from the index finger. Four patients had oesophageal pressure monitoring during the study. The records were scored using Rechtschaffen and Kales criteria[17]. Apnoeas were determined as an absence of air flow, by monitoring device output, for 10 seconds or greater. Apnoeas were characterized as obstructive if chest or abdominal movement continued during the event. Hyponoeas were determined by a greater than 50% decrease without absence of airflow in air flow measures for 10 seconds or greater. The respiratory disturbance index (RDI) was calculated as the number of apnoeas plus hyponoeas per hour. Patients were determined to have sleep apnoea if the respiratory disturbance index was greater than 10 events per hour. Continuous positive airway pressure (CPAP) was initiated during the first night of study if the patients exhibited prolonged apnoeas with heart rate less than 55 beats per minute and oxygen desaturation below 75% in the first two hours of the polysomnogram. Patients who did not exhibit this severity were observed for the remainder of the night and had a CPAP trial on a second night if the apnoea was not related to position. CPAP was titrated to the normalization of the patient's respiration in the supine position during REM sleep and to maintain oxygen saturation above 90%. The patients were subsequently treated as outpatients for their OSA with either positional therapy or CPAP based on the overnight polysomnogram. Each patient's seizure frequency and anticonvulsant regimen were followed for at least one year following the institution of therapy. Seizure frequency was calculated by patient report on seizure calendars. Anticonvulsant levels were obtained before and following the institution of therapy for the OSA.

Correlation statistics were performed using Pearson Product–Moment correlation with significance determined as a P value of less than 0.05.

RESULTS

The subjects ranged in age from 21 to 79 years. Only one of the subjects was female. One patient had a primary generalized epilepsy and the remaining patients had partial seizures. Nine of the subjects were referred for evaluation and therapy of a known seizure disorder. The remaining subject was referred for a evaluation of unusual nocturnal spells and was subsequently diagnosed with epilepsy.

All the subjects noted snoring and symptoms of excessive daytime sleepiness or unrefreshing sleep. Only one patient was referred with a known diagnosis of OSA. None of the subjects had craniofacial abnormalities such as micrognathia or retrognathia, or hypothyroidism which would contribute to airway obstruction. A wide variety of sleep stages percentages and latencies were found among the patients (Table 1). Three patients (Patients 1, 2 and 10) had CPAP initiated on the first night of study due to bradycardia or severe oxygen desaturations associated with apnoeas (Table 1).

Four of the patients improved with treatment of the sleep apnoea alone. Three of these patients (Patients 2, 3 and 4) became seizure free and a fourth patient (Patient 1) had a greater than 95% reduction in seizure frequency following the initiation of therapy for the sleep apnoea without any change to the anticonvulsant regimen. Three of these four patients had a state dependent seizure pattern (Patient 1, awakening and Patients 3 and 4, sleep related). Three patients of this group had partial seizures ranging in frequency of two per year to three per month. The remaining patient had daily bouts of myoclonic seizures. These four responders ranged from mild to severe OSA. Two of the four responders exhibited the

Table 1: Sleep stage parameters from the diagnostic sleep study from ten patients.

Patient number	Sleep efficiency (%)	Total sleep time (minutes)	Sleep latency (minutes)	REM latency (minutes)	Awake (%)	Stage 1 (%)	Stage 2 (%)	Stage 3&4 (%)	REM (%)	CPAP started on first night
1	72	305	45	112	16	13	16	31	22	Yes
2	87	351	1	121	12.5	17	28	24	18	Yes
3	55	237	36.5	52	39	5	31	18	7	No
4	71	280	5	243	28	9	44	13	7	No
5	98	354	2	243	2	14	54	25	5	No
6	73.5	322	28	390	19	63	13	3	1	No
7	90	355	4	144	8	11	55	18	8	No
8	95	69	1	249	1	12	50	27	7	No
9	65.5	272	36.5	183	27	19	22	27	4	No
10	64	261	17.5	287	30	8	24	32	5	Yes

REM, Rapid eye movement sleep.

typical body habitus for OSA. The other two responders (Patients 3 and 4) weighed under 200 pounds and did not exhibit any physical features suggesting upper airway obstruction. These patients were treated with positional therapy based on significant improvement of the OSA observed with the patients assuming the lateral decubitus position (Table 2).

Three patients improved with medication change and treatment of the OSA. Patient 5, who was on valproate, had phenobarbital added as a second medication, one month prior to the institution of CPAP. His seizure frequency went from an average of four seizures per month for the year to two seizures the month prior to CPAP. This patient improved further following treatment of OSA having had only one seizure in the year since the initiation of CPAP. Patient 6 had an increase in phenobarbital one month prior to the institution of the CPAP. This patient's last seizure occurred three weeks prior to starting CPAP, and he has been seizure-free for 14 months. The third patient (Patient 7) was averaging one seizure per three months, prior to the treatment of the OSA. This patient had one seizure six months following the initiation of CPAP and subsequently started anticonvulsant therapy. This patient has since been seizure-free for one year.

Three patients (Patients 8, 9 and 10) had less than a 50% reduction in seizure frequency. All three of these patients had state independent pattern to their seizures. One of the non-responders (Patient 9) tried CPAP, but was unable to tolerate this therapy after two months. The patient's overnight polysomnogram demonstrated some improvement but not total resolution of the sleep apnoea with the patient in the lateral decubitus position. We opted for positional therapy as an alterantive treatment for this patient, knowing that the lateral decubitus position did not totally resolve the OSA. The patient also lost 62 pounds but neither of these manoeuvres were associated with improvement in seizure frequency. However, this patient did have subjective benefit in daytime sleepiness and declined further objective testing.

Review of sleep parameters compared to seizure improvement revealed the seizure percent improvement of the seizure frequency did not correlate with the RDI ($r = -0.23$) or sleep efficiency ($r = 0.10$) even with removing the patients who received CPAP the first night.

DISCUSSION

Sleep disruption or oxygen desaturation from OSA could exacerbate an underlying seizure disorder. Improvements in sleep quality will decrease seizure frequency in some patients[18]. Four of our patients (40%) reduced the frequency of recurrent seizures solely with the treatment of the OSA and an additional three patients improved with adjustments of anticonvulsant medication combined with treatment of their OSA. This improvement may have resulted from avoiding severe oxygen desaturation at night or the improved sleep quality by the elimination of the periodic arousals evoked by the obstructive apnoeas. However, neither the severity of apnoea nor the type of treatment for OSA appeared to be a consistent factor amongst the group of responders.

In our series, the lack of severe oxygen desaturation in many of these patients suggests the oxygen desaturation is not the principal factor in exacerbating the seizures. Four of our patients

Table 2: OSA and seizure data from ten patients.

Patient number	Age (years)	Weight (pounds)	Respiratory disturbance index/hours	Lowest oxygen desat. %	Type of therapy for OSA	Medications and levels prior to Rx (mcg/ml)	Medications and levels following Rx (mcg/ml)	Type of epilepsy	Relationship of seizures to sleep	Seizure frequency prior to Rx	Seizure frequency following Rx
1	28	302	42	74	CPAP	Valproate (93)	Valproate (89)	Juvenile myoclonic	Awakening	Daily bouts of myoclonus	1 in 1 year
2	41	241	106	55	CPAP	Phenytoin (11)	Phenytoin (10)	Complex partial	Diffuse	3/month	0 in 2.5 years
3	79	185	37 5 lateral decub (48/hr supine)	88	Positional	Phenytoin (5)	Phenytoin (7)	Complex partial	Sleep	3/year	0 in 2.8 years
4	38	148	11 2 lateral decub (21/hr supine)	88	Positional	Phenytoin (14)	Phenytoin (10)	Complex partial	Sleep	2 year	0 in 2 years
5	28	300	48	65	CPAP	Valproate (110)	Valproate (88) Phenobarital (19)	Complex partial	Diffuse	2/month (see text)	1 in 1 year
6	55	210	91	53	CPAP	Phenobarbital (12)	Phenobarbital (20)	Complex partial	Diffuse	10 month	0 in 1 year
7	45	273	46	72	CPAP	None	Initially no medicines Subsequently phenytoin was added (7)	Complex partial	Sleep	1 3 months	Initially one in 6 months. Seizure free with Phenytoin
8	42	285	60	82	CPAP	Carbamazepine (5.8) Phenytoin (28)	Carbamazepine (9.0) Phenytoin (21)	Complex partial	Diffuse	4/month	4/month
9	21	280	20 7.5 lateral decub (48/hr supine)	87	CPAP/ Positional	Phenytoin (17) Carbamazepine (8.6) Valproate (121)	Phenytoin (25) Valproate (75) Felbamate (3600)	Complex partial	Diffuse	6/month	7/month
10	51	300	>120	77	CPAP	Carbamazepine (14.6) Phenobarbital (40)	Carbamazepine (14.1) Phenobarbital (34)	Complex partial	Diffuse	15/month	11.5/month

Rx, Treatment for OSA.

did not have oxygen desaturation below 80%. The desaturation in these cases clearly can not account for the recurrence of seizures unless the patients had more severe nocturnal oxygen desaturations than recorded. This is possible but is improbable, particularly in the patients with relatively thin body habitus, since these patients have adequate pulmonary functional reserve capacity.

Sleep disruption and sleep deprivation may be factors in exacerbating seizures in these patients. Sleep disruption would also lead to increased sleep/wake transitions which may in itself increase the likelihood of seizures. Sleep disruption related to the sleep apnoea may be estimated by the RDI. Percent improvement of the seizure frequency did not correlate with the RDI or sleep efficiency. This may indicate that any disruption of sleep or increase in sleep wake transitions greater than a certain level might exacerbate the underlying seizure disorder in specific epileptic patients.

Although obesity is a common feature in patients with symptoms of OSA, two of the patients, who improved with treatment of their sleep apnoea, were not obese. Patients exhibiting normal body habitus have been found to have OSA, and a more subtle form of night-time airway obstruction, upper airway resistance syndrome[19]. Upper airway resistance syndrome can produce similar daytime sequelae as OSA.

Many types of epilepsy increase sleep disturbance[20]. These are usually marked by increase number of stage changes and arousals. Epilepsy, however, has not been reported to increase the risk of OSA, but large population studies have not been performed to adequately assess the prevalence of OSA in epileptic patients.

Medications may have an affect upon sleep apnoea. Similar to benzodiazepines and alcohol, barbiturates decrease the tone of upper airway muscles and thus increase upper airway obstruction during sleep[21]. Three patients were prescribed phenobarbital and two of these patients improved with the addition of CPAP and medication adjustment. Valproate may also exacerbate a tendency for OSA by the enhancing weight gain. However, only one patient of three on valproate (Patient 9), noted any weight gain with the medication and this patient did not improve in seizure frequency once treated for the OSA.

In general, seizures in patients with state dependent types of epilepsy are more likely to respond to anticonvulsant therapies than those with a state independent epilepsy, as reported by Janz[3]. Three of the four patients, who improved with only treatment of the OSA, had epilepsy which was dependent upon the sleep or awake state. One of the three patients, who improved with adjustment to medication and treatment of the OSA, had a state-dependent pattern of epilepsy. Forty percent of our study population had a state-dependent pattern to their seizures and this may have skewed our results. Yet, three of the patients who improved (one with CPAP alone, two with CPAP and medication) had state independent patterns of epilepsy. Conversely, all of the non-responding epileptic patients had a state-independent pattern to their epilepsy. The lack of state dependence of their seizures may indicate their foci are less influenced by the environmental changes produced by sleep and sleep disorders. In this context, one would predict that patients with state independent epilepsy would be less likely to improve in seizure frequency following improvement in sleep quality.

Regardless of the mechanism, we feel OSA should be considered as a possible exacerbating factor in patients with epilepsy. All epilepsy patients, despite body habitus, should be questioned for symptoms of OSA or other forms of sleep disturbance. The possibility of sleep disturbance should not be overlooked, particularly in patients failing to respond to treatment. Evaluation and treatment of epileptic patients with OSA should be pursued to improve the frequency of recurrent seizures and the symptoms directly attributable to the OSA.

REFERENCES

1. Passouant, P. Historical aspects of sleep and epilepsy. *Epilepsy Research* 1991; **Suppl. 2:** 19–30.
2. Janz, D. The Grand Mal epilepsies and the sleeping–waking cycle. *Epilepsia* 1962; **3**: 69–109.
3. Janz, D. Epilepsy and the sleep–waking cycle. In: (Eds. P.J. Vinken and G.W. Bruyn). *The Epilepsies, Handbook of Clinical Neurology.* Amsterdam, North Holland Publishing Company 1974: **15**: 457–490.
4. Ellinson, R.J. Wilkin, K. and Bennett, D.R. Efficacy of sleep deprivation as an activation procedure in epilepsy patients. *Journal of Clinical Neurophysiology* 1984; **1**: 83–101.
5. Degen, R. and Degen, H.E. Sleep and sleep deprivation in epileptology. *Epilepsy Research* 1991; **Suppl. 2**: 235–260.
6. Thomaides, T.N., Kerezoudi, E.P., Chaudhuri, L.R. and Cheropoulos, C. Study of EEG's following 24-hour sleep deprivation in patients with post-traumatic epilepsy. *European Neurology* 1992; **32**: 79–82.

7. Rajna, P. and Veres, J. Correlations between night sleep duration and seizure frequency in temporal lobe epilepsy. *Epilepsia* 1993; **34**: 574–579.
8. Veldhuizen, R., Binnie C.D. and Beinttema, D.J. The effect of sleep deprivation on the EEG in epilepsy. *Electroencephalography Clinical Neurophysiology* 1983; **55**: 505–512.
9. Gibbs, E.L. and Gibbs, F.A. Diagnostic and localizing value of electroencephalographic studies in sleep. *Research Publications—Association for Research in Nervous and Mental Disease* 1947: 26, 366–376.
10. Halasz, P. Sleep, arousal and electroclinical manifestations of generalized epilepsy with spike wave pattern. *Epilepsy Research* 1991; **Suppl. 2:** 43–48.
11. Wieser, H.G. Temporal lobe epilepsy, sleep and arousal: stereo-EEG findings. *Epilepsy Research* 1991; **Suppl. 2:** 97–119.
12. Partinen, M. and Telakivi, T. Epidemiology of obstructive sleep apnea syndrome. *Sleep* 1992; **15**: S1–4.
13. Kryger, M. Quesney, L.F., Holder, D., Gloor, P. and MacLeod, P. The sleep deprivation syndrome of the obese patient, a problem of periodic nocturnal upper air way obstruction. *American Journal of Medicine* 1974; **56**: 531–538.
14. Wyler, A.R. and Weymuller, E.A. Epilepsy complicated by sleep apnea. *Annalsis of Neurology* 1981; **9**: 403–404.
15. Vaughn, B., Messenheimer, J.A., D'Cruz O. and Beach R.L. Sleep apnea in patients with epilepsy. *Epilepsia* 1993; **34** (Suppl. 6): 136.
16. Devinsky, O., Ehrenberg, B., Barthlen, G.M., Abramson, H.S. and Luciano, D. Epilepsy and sleep apnea syndrome. *Neurology* 1994; **44**: 2060–2065.
17. Rechtschaffer, A. and Kales, A., eds. *A Manual for Standardization Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects.* Bethesda, NIH Publication 204 bis, US Government Printing Office, 1968.
18. Aird, R.B. The importance of seizure inducing factors in youth. *Brain Development* 1988; **10**: 73–76.
19. Downey III, R., Perkin, R. and MacQuarrie J. Upper airway resistance syndrome: sick, symptomatic but underrecognized. *Sleep* 1993; **16**: 620–623.
20. Touchon, J., Baldy-Moulinier, M., Billiard, M., Besset, A. and Cadilhac, J. Sleep organization and epilepsy. *Epilepsy Research* 1991; **Suppl. 2:** 73–81.
21. Hishikawa, Y., Furuya, E. and Wakamatsu, H. Hypersomnia and periodic respiration-presentation of two cases and comment on physiopathogenesis of the Pickwickian syndrome. *Folia Psychiatrica et Neurologica Japonica* 1970; **24**: 163–173.