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Epilepsy and Obstructive Sleep Apnea

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Key Words
Epilepsy · Obstructive sleep apnea · Seizure control · Continuous positive airway pressure treatment · Excessive daytime sleepiness

Abstract
A few publications documented the coexistence of epilepsy and obstructive sleep apnea (OSA). The extent, nature, and clinical relevance of this association remain poorly understood. We retrospectively reviewed the database of our sleep center to identify patients with both sleep apnea and epilepsy. Characteristics of epilepsy, sleep history, presence of excessive daytime sleepiness [Epworth Sleepiness Scale (ESS)] and polysomnographic data were assessed. The effect of continuous positive airway pressure (CPAP) on seizure reduction was prospectively analyzed after a median interval of 26 months (range: 2–116 months) from the diagnosis of OSA. OSA was found in 29 epilepsy patients (25 men and 4 women) with a median age of 56 years (range: 37–79). The median apnea hypopnea index was 33 (range: 10–85), the oxygen desaturation index was 12 (range 0–92), and 52% of the patients had an ESS score >10. In 27 patients, epilepsy appeared 1 month to 44 years prior to the diagnosis of OSA. In 21 patients, the appearance of OSA symptoms coincided with a clear increase in seizure frequency or the first appearance of a status epilepticus. Treatment with CPAP was continued with good compliance in 12 patients and led to a significant reduction of both ESS scores and seizure frequency in 4 patients. Our data suggest the importance of considering diagnosis and treatment of OSA in epilepsy patients with poor seizure control and/or reappearance of seizures after a seizure-free interval.

Introduction

The presence of obstructive sleep apnea (OSA) has been found in 5–63% of patients with epilepsy. Frequency rates were higher in patients with refractory epilepsy or epilepsy patients referred to a sleep center [1–4] and lower [5–7] in unselected populations.

The pathogenesis, clinical relevance and therapeutical consequences of the association between OSA and epilepsy remain, however, poorly known. Devinsky et al. [8] described an improved seizure control in 2 out of 5 patients with epilepsy and OSA under continuous positive airway pressure (CPAP) treatment. In 3 different case series (all together 30 patients), a beneficial effect of CPAP on seizure control was reported in about 40% of patients [3, 9, 10]. Among 63 epilepsy patients who underwent

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Table 1. Outcome of CPAP treatment in patients with OSA and epilepsy (previous and present studies)

Author	Year	Patients with OSA and epilepsy	OSA definition	Patients with CPAP/BIPAP	Good compliance	Seizure reduction with CPAP
Devinsky et al. [8]	1994	7	range 26–73/h	5/7	2/5	2/2
Vaughn et al. [9]	1996	10	AHI ≥ 5/h	8/10	7/8	1/7
Sonka and Nevsimalova [10]	1997	11 (adult patients) 2 (pediatric patients)	AHI ≥ 10/h or ODI ≥ 10/h[b] (≥ 4% SaO_2 decrease)	4/11	2/4	1/4
Malow et al. [2]	1997	44	AHI ≥ 10/h	28/44	15/28	3/15
Beran et al. [3]	1999	15	not specified	13/15	7/13	4/7
Malow et al. [1]	2000	13	AHI ≥ 5/h	5/13	0	not evaluable
Malow et al. [7]	2003	6[a] (adult patients) 3[a] (pediatric patients)	AHI ≥ 10/h AI ≥ 1/h or ODI >1.5/h (≥ 4% SaO_2 decrease)	5/6 3[c]/3	3/5 1/3	3/3 1/1
Present study		29	AHI ≥ 10/h	23/29	12/23	4/12

AI = Apnea index (used for children); BIPAP = bilevel positive airway pressure.

[a] Only patients with at least four seizures a month and a pathological score on the Sleep Apnea Scale of the Sleep Disorders Questionnaire were included.

[b] Respiratory polygraphy was used for OSA diagnosis.

[c] Two of the 3 patients were also treated with vagus nerve stimulator.

polysomnography (PSG) in a sleep center, OSA was diagnosed in 44 patients [2]. In 28 out of those 44 patients CPAP was prescribed and in 15 of them good compliance was achieved. A reduction in seizure frequency without concomitant changes in antiepileptic drug (AED) treatment was observed in 3 out of these 15 patients [2]. So far, only one prospective study assessed the effect of CPAP treatment on seizure frequency [7]. In 62 (14%) out of 444 patients, the presence of OSA was suspected on the base of a validated questionnaire. Only patients with at least four seizures/month and a PSG-confirmed OSA defined by an apnea hypopnea index (AHI) ≥ 10/h (n = 6) were treated with CPAP (n = 5) or oral appliance (n = 1). Seizure frequency was prospectively monitored while AEDs were kept stable. An overall 45% seizure reduction was observed in 3 out of 5 adults and in 1 child with good compliance to CPAP treatment [7].

The overall clinical relevance of OSA and of its treatment for seizure control remain uncertain. In particular, the number of patients with epilepsy and OSA and effective treatment is limited in the literature (overall 40 patients; table 1) and there are only three case reports [11–13]. The main aims of the present study were therefore: (1) to estimate the frequency of the combined occurrence of seizure and OSA; (2) to assess the temporal and causal relationship between seizure occurrence and onset/development of OSA symptoms, and (3) to test the effect of CPAP treatment on seizure control.

Methods

Study Design

The study was divided into a retrospective and a prospective part. The retrospective part consisted of a 7-year review (1992–1999) of our database to identify patients with a diagnosis of both OSA and epilepsy (at least two unprovoked seizures). All epilepsy patients with OSA entered the prospective part of the study. The primary goal of the prospective part was to study the effect of CPAP therapy on frequency of epileptic seizures. All epilepsy patients with OSA were followed by regular clinic visits beginning at the latest at the time of the first PSG recording. Follow-up visits (with or without EEG, revision of seizure diary, sleep tests) as well as treatment adjustments were chosen individually based on clinical judgement. Diagnostic PSG and indication of CPAP therapy were assessed retrospectively from our database and precluded the need of approval by the local ethics committee. Clinical follow-up was indicated in all of the participants and part of routine counselling.

OSA Assessment

The presence and onset of loud habitual snoring, weight gain and witnessed apneas were assessed by history. The presence and severity of excessive daytime sleepiness (EDS) were estimated by means of the Epworth Sleepiness Score (ESS) in 25 patients [14]. All-night diagnostic PSG (Neurofax 5500 G®) in our sleep laboratory included the following parameters: two EEG channels (O1-A2, C4-A1), two electrooculograms (vertical and horizontal), four EMG recordings (submental, masseter, and tibialis anterior muscle of both sides), electrocardiogram, oronasal flow (thermistor), thoracoabdominal movements (Respitrace®) and oxymetry (Ohmeda Biox®). The data were stored on a PC for off-line analysis (Nicolet Ultrasom 2.1®). Sleep stages were scored according to Rechtschaffen and Kales using 30-second epochs. OSA was defined by an AHI >10/h. The oxygen desaturation index (ODI) was calculated by the number of desaturations (defined by a decrease of 4% or greater compared to baseline) divided by hours of total sleep time. Sleep stages, apneas, hypopneas and oxygen desaturations were scored automatically and visually corrected when necessary.

Epilepsy Assessment

Type, etiology, sleep association and frequency of epileptic seizures as well as current AED treatment were noted. According to the suggestion of Vaughn et al. [9] sleep-associated epilepsy was defined by the presence of seizures occurring during sleep or in the first 2 h after awakening, whereas sleep-independent seizures occur in a diffuse distribution independent of the sleep/wake state. Wake EEG was obtained at least once in all patients. Frequent seizures were defined as one or more seizures per month. Improved seizure control was defined as a reduction of seizures of at least 50% due to therapeutic intervention (AEDs or CPAP).

Follow-Up with CPAP

Response to CPAP treatment on seizure frequency and EDS was noted. Good compliance with the CPAP device was defined as the use of the device for more than 4 h per night and for more than 70% of the observed nights [15]. Compliance with CPAP treatment and changes of EDS were assessed by clinical interview and by the ESS. Seizure diaries were reviewed and checked for secondary seizures related to established risk factors including intermittent disease, sleep deprivation, drug and alcohol abuse, interaction with other medication and noncompliance. Blood samples were taken from patients who were treated with AEDs (all but 1 patient) to control for AED compliance.

Relationship OSA-Epilepsy

Time of epilepsy diagnosis and time of OSA diagnosis (i.e. date of PSG) were noted. Furthermore, it was assessed whether onset of OSA symptoms (such as EDS, witnessed apneas, or loud habitual snoring) coincided, preceded or followed changes in seizure control (e.g. new onset of seizures, increase in seizure frequency, or occurrence of a status epilepticus). Similarly, seizures worsening to factors not related to OSA were estimated. A relationship between OSA and epilepsy was considered likely when (1) onset of OSA symptoms coincided with a change in seizure control, and/or (2) CPAP treatment led to a reduction in seizure activity of $\geq 50\%$ compared to baseline (defined here as the seizure frequency observed 3–6 months preceding CPAP). Conversely, a direct relationship between the two disorders was considered unlikely if one or both conditions mentioned above were not satisfied. In a third group of patients, the nature of the relationship between OSA and epilepsy remained undetermined based on insufficient or questionable data.

Statistics

Appropriate group statistics were performed using the Wilcoxon signed rank test or the Mann-Whitney test.

Results

Co-Occurrence of OSA and Epilepsy

During the 7-year period, OSA was diagnosed by PSG in 557 patients. All patients were primarily referred because of sleep-wake disturbances (EDS, insomnia, disturbed sleep). In 29 (5%) of them, a diagnosis of epilepsy was also made. There were 25 men and 4 women, with an age range of 37–79 years (median: 56 years). The BMI ranged from 20 to 48 (median: 28).

Obstructive Sleep Apnea

The AHI ranged from 10 to 85 (median: 33). Fourteen patients (56%) had moderate to severe OSA as defined by an AHI greater than 40. The ODI ranged from 0 to 92 (median 12/h). Thirteen (52%) out of 25 patients had an ESS score >10, and 7 of them had an ESS score >15. The follow-up time after the diagnosis of OSA ranged from 2 to 116 months (median: 26 months).

Epilepsy

Seizure type was generalized (mostly tonic-clonic seizures) in 20 patients and focal in 9 patients. Epilepsy was symptomatic in 12 patients and included such diagnoses as stroke (n = 1), brain abscess (n = 2), cerebral hypoxia (n = 1), brain tumor (n = 1), perinatal damage (n = 3), and traumatic brain injury (n = 4). Epilepsy was sleep-associated in 8 patients (cases 5, 7, 11, 18, 21, 23, 26, and 28). All but 1 patient (case 17) were treated with AEDs, mostly monotherapy (n = 21), bitherapy (n = 6), and tritherapy (n = 1). Frequent seizures (>1/month) were observed in 9 patients. For details of AED treatment and of PSG results, see table 2.

Time of Diagnosis of OSA and Epilepsy

Epilepsy was diagnosed *prior to* the PSG diagnosis of OSA (range 1 month to 44 years, median 108 months) in 27 patients.

In 21 out of these 27 patients, a change in seizure control onset was considered likely with the onset of OSA symptoms. Two out of the 21 patients (cases 2 and 16) had a new-onset status epilepticus after having been sei-

Table 2. Clinical characteristics and PSG data of epilepsy patients with OSA

No.	Age/sex	BMI	ESS	AHI	ODI	CPAP	Seizure type	Seizure frequency	AED	Interval of diagnoses, months
1	52/m	41.2	16	70	33	yes	GTCS	2/month	VPA	8
2	51/f	48	17	65	85	yes	GTCS	status	PHT, PB	336
3	79/m	23.1	n.a.	65	19	no	GTCS	3/year	PHT	–9[b]
4	55/f	33.9	7	22	1.7	no	GTCS	seizure-free since 15 years	CBZ	528
5	62/m	27.8	13	13	2.3	yes	GTCS	1/month	PHT	24
6	43/m	32.4	13	50	44	yes	PCS	2 seizures since 8 years	VPA	48
7	67/m	27	5	31	0	yes	GTCS	3 seizures	CBZ	18
8	64/m	25.9	11	44	41	yes	PCS	2/week	VPA, PHT	108
9	63/f	27.3	6	20	n.a.	yes	PCS	3 seizures	PHT, CBZ	1
10	54/m	42.6	14	51	5.8	yes	GTCS	2 seizures	VPA	132
11	47/m	28.4	2	25	6.5	yes	PCS	1/month	PHT, VPA	168
12	66/m	31.5	5	27.1	16	yes	PS	1/month	CBZ	84
13	73/m	30.9	n.a.	61	74	yes	GTCS	<1/year	PB	108
14	56/m	33.3	7	85	92	yes	GTCS	<1/year	CBZ	120
15	53/m	31.1	16	13	n.a.	yes	GTCS	1/year	VPA	372
16	52/m	42.5	19	74	53	yes	pGTCS	status	BBX	480
17	51/m	30.3	14	44	n.a.	yes	PCS	1/week	none	132
18	37/m	28.1	n.a.	41	50	yes	PCS	3/day	CBZ, PHT, GBP	420
19	58/m	25	21	44	21	yes	PCS	seizure-free since 6 years	CBZ	144
20	50/m	24.9	6	10	0.5	no	GTCS	1/month	PHT, BBX	180
21	60/f	20	18	15	0.3	yes	GTCS	½ month	VPA	14
22	64/m	26.8	10	18	0.9	yes	GTCS	2 seizures	CBZ	156
23	60/m	27.8	5	31	0.2	no[a]	GTCS	7 seizures	VPA	72
24	52/m	32.5	19	71	86	yes	PCS	3 seizures	VPA	–12[b]
25	45/m	35.7	4	44	14	yes	GTCS	3/year	CBZ	348
26	66/m	23.7	0	20	5.9	no[a]	GTCS	5 seizures	VPA	11
27	54/m	22.7	n.a.	18	1	no[a]	GTCS	1/year	PHT	324
28	61/m	24.3	10	33	9.7	yes	GTCS	1/month	PHT, CBZ	18
29	56/m	25.2	11	14	0	yes	GTCS	3 seizures	VPA	12

pGTCS = Primary generalized tonic clonic seizure; PCS = partial complex seizures; PS = partial seizure; VPA = valproic acid; CBZ = carbamazepine; PHT = phenytoin; PB = phenobarbital; GBP = gabapentin; BBX = barbexaclone.

[a] CPAP was planned.

[b] Minus sign indicates that epilepsy followed OSA diagnosis.

zure-free for years with and without AEDs, respectively. Nine out of the 21 patients showed a first onset of seizures. In the remaining 10 out of the 21 patients, an increase in seizure frequency was noted despite AEDs. In 7 out of the 27 patients (patients 2, 4, 15, 16, 18, 25, and 27), an especially long interval between onset time of epilepsy and time of OSA diagnosis was found (>300 months). ESS scores and AHI were similar in these 7 patients to the other 20 patients of this group (data not shown). In 2 patients (patients 3 and 24), epilepsy was diagnosed *after* the diagnosis of OSA (9 and 12 months, respectively). In patient 3 with tetraplegia after spinal cord injury, severe OSA was diagnosed after referral for a first generalized tonic-clonic seizure. Nine months later, another unprovoked generalized seizure occurred and thus allowed the diagnosis of epilepsy. Patient 24 had several secondary generalized seizures that occurred first 1 year after the beginning of CPAP treatment. A control PSG under CPAP treatment showed an AHI of 4 and a normalization of the ESS score (from 19 before to 3 after CPAP).

Follow-Up with CPAP

CPAP therapy was prescribed in 23 patients and good compliance (≥ 4 h/night) was obtained in 12 of them. In these 12 patients, a significant effect of CPAP on the ESS score was found (Wilcoxon signed rank test for ESS before

versus after CPAP treatment: $p = 0.002$). In the subgroup with an ESS score >10, CPAP treatment led to a significant ESS score reduction [median ESS score of 16 before and 8 after treatment, respectively; $p = 0.003$ (Wilcoxon signed rank test)]. In the subgroup with an ESS score <10, CPAP treatment showed a nonsignificant ESS score reduction (median ESS scores before and after CPAP treatment of 6 and 3, respectively; $p > 0.05$). In 4 out of the 12 patients, both a clear reduction of the ESS score and seizure frequency was observed with CPAP (cases 15–17 seizure-free, case 18 significant reduction in seizure frequency). Case 17 was the only patient in the present series without AED treatment, and became seizure-free after the beginning of CPAP therapy, thus eliminating the need for AED treatment. Despite clinical improvement, EEG remained abnormal with spike-wave-activity in cases 15 and 16. Hence, a positive therapeutic effect of CPAP on seizure control was considered likely in 4 out of the 12 patients treated. In 4 other patients, this effect was considered unlikely. In the remaining 4 patients, the effect of CPAP on seizure frequency remained undetermined/unclear for different reasons (lost to follow-up, seizure-free already with AEDs).

Discussion

The main results of our study are: (1) the observation of a higher than expected co-occurrence of OSA and epilepsy in a series of patients investigated because of sleep-wake disturbances, and (2) the suggestion of a causal link between OSA and seizure frequency in a considerable percentage of epilepsy patients with OSA. The advantages of this study are: (a) a selective large sample of epilepsy patients with OSA who were treated with CPAP (table 1), and (b) the prospective follow-up of patients who complied with CPAP therapy. These factors allowed us to better estimate the effect of CPAP treatment on seizure control.

Co-Occurrence of Epilepsy and OSA

The observed coexistence of OSA and epilepsy in 5% of our study sample is higher than co-occurrence of both diseases expected by chance. Assuming a lifetime prevalence of 1.8% for epilepsy [16] and 2–4% for OSA of the general population [17], the two diseases should co-occur by chance in approximately 0.04–0.08% of the population. Obviously, our data represent only a rough approximation of the 'true' co-occurrence of both diseases mainly because of our patients' selection. Epilepsy patients referred to a sleep laboratory are preselected for evaluation of sleep disorders, including OSA. Nevertheless, our data are in line with previous studies that reported a frequency of OSA in up to 30% of epilepsy patients [1, 5, 18, 19].

Causal Link between OSA and Seizure Frequency

The high frequency of OSA among epilepsy patients suggests a link between both diseases. Our study gives insights into the nature of this link. First, we found a possible temporal relationship between onset of OSA symptoms and change in seizure control in about two thirds of our patients. The change in seizure control consisted of an increase in seizure frequency, first onset of seizures or new onset of status epilepticus. Previous studies documented the coexistence of epilepsy and OSA. Our study differs from these studies in that for the first time we analyzed the temporal relationship of seizure frequency and OSA diagnosis. Of importance is the fact that other explanations for a poor seizure control were not present. Patients were, in particular, on stable dosages of AEDs and no risk factors other than OSA could be identified. In epilepsy, the mechanism of 'spontaneous' seizure fluctuations remains largely unknown. Sleep deprivation, poor compliance in long-term AED treatment, interaction with concomitant medications and intercurrent (febrile) diseases are established triggers of new-onset seizures or status epilepticus even in patients who have remained seizure-free for years. Our observations suggest that OSA might be another factor that may lead to a worsening in seizure control. Second, in the prospective part of our study, effective CPAP therapy could be initiated and maintained in 12 out of 23 patients with both OSA and epilepsy. CPAP treatment led to a significant reduction in seizure frequency in 4 out of the 12 patients. Our findings support the hypothesis that CPAP therapy may improve seizure frequency in compliant patients. The rate of 30% seizure reduction is similar to the responder rate of 20% of Malow's sample [2] but lower compared to previous studies in which a seizure reduction of up to 100% was reported (table 1). However, as illustrated in table 1, the very high rates of CPAP-compliant patients exhibiting an improvement in seizure control are only observed in small case series [18]. In addition, most of the studies are biased by their retrospective design [8, 9, 20]. The largest prospective study so far published screened 398 adult epilepsy patients for OSA. Only 3 out of 5 patients with OSA and epilepsy who complied with CPAP therapy had a reduction of 43% in the frequency of complex partial seizures and of 73% in the frequency

of atonic seizures [7]. Due to the small number of patients treated with CPAP so far, no consistent factors have been identified that may predict a favorable effect of CPAP on seizure frequency. The present study suggests EDS but not severity of OSA (as estimated by the AHI) or presence of epileptic activity on EEG as factors that may herald improved seizure control with CPAP. The presence of EDS may in fact positively affect CPAP compliance [21]. On the other hand, sleep deprivation and as a consequence EDS are well known to decrease seizure threshold, although this effect may not be invariably present in each patient subgroups and forms of sleep deprivation/disruption [22]. This study suffers from major limitations, which mainly relate to the retrospective analysis of the temporal evolution of OSA symptoms and seizure control, and the limited number of patients studied. Considering the gradual onset of OSA in many patients, the temporal relationship of OSA to seizure frequency should be regarded as an approximation and not as an exact time of OSA onset. Therefore, we cannot exclude that we have missed other relevant factors contributing to poor seizure control. However, among several potential factors, diagnosis and treatment of OSA are feasible, whereas other factors involved in 'spontaneous' seizure fluctuation remain largely unknown. The success rate in seizure reduction with CPAP therapy in compliant patients supports a causal relationship between seizure occurrence and OSA symptoms. Seizure reduction under CPAP therapy may be biased by a 'floor effect' as baseline seizure frequency in some patients was too low to measure improvement (table 2). Finally, as we did not control for placebo effects by using sham CPAP, we cannot comment on the effect of CPAP intervention compared to random seizure fluctuations. Multicenter studies with randomized placebo-controlled designs are needed to recruit a sufficient number of patients and to further investigate the interaction of OSA and epilepsy.

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