

Excessive Daytime Sleepiness and Sleep Disorders in a Population of Patients with Epilepsy: a Case-Control Study

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Background and Purpose: There are several primary causes for excessive daytime sleepiness (EDS) and sleep disorders in patients with epilepsy. Up to now, studies in the literature report conflicting data in terms of both prevalence and aetiology. The aim of our study was therefore to evaluate the prevalence of EDS and some sleep disorders in a population of patients with epilepsy treated with no more than two antiepileptic drugs (AEDs). We also investigated the role of the depression of mood as a variable that can negatively affect EDS.

Methods: We prospectively and consecutively recruited 99 patients with a diagnosis of epilepsy, sleep disorders and EDS, belonging to the Centre for Epilepsy of the Department of Experimental Biomedicine and Clinical Neurosciences of the University of Palermo. 61.6% of patients recruited were suffering from focal epilepsy, and 38.3% from generalized epilepsy. 68.6% were undertaking monotherapy and 27.2% were drug resistant. Patients were matched for sex and age (+/- 5 years) with 96 non epileptic controls recruited from high school students, college students, relatives and friends of the medical team that conducted the study.

EDS was found in 11.1% of patients with epilepsy. Clinical evaluation of sleep disorders was performed using validated questionnaires to investigate excessive daytime sleepiness (EDS), insomnia, Restless Legs Syndrome (RLS) and Obstructive Sleep Apnoea Syndrome (OSAS). In a second phase of the study, 43 of the investigated patients and 34 controls - after giving their consent - underwent a polysomnographic examination by "Compumedics Somtè".

Results: Our study shows a statistically significant difference between cases and controls with regard to the prevalence of RLS ($p = 0.022$) and severity of OSAS with an increased risk in moderate-severe forms of epilepsy (odd ratio [OR] 2.5) most significantly associated with male gender ($p = 0.04$) and focal epilepsy (OR 3.8) with PSG seizures (0.02). Moreover, a statistically significant difference was demonstrated about mood disorders ($p = 0.001$) among patients with epilepsy and non epileptic controls. Sleepiness in patients with epilepsy seems to be particularly related to both the depression of mood ($p = 0.01$) and the presence of OSAS ($p = 0.03$), as well as to a higher mean age ($p = 0.006$) and a longer duration of illness ($p = 0.04$).

Conclusions: Our results confirm that drowsiness trouble frequently complained by patients with epilepsy, is particularly related not only to the presence of OSAS but also to the depression of mood. (2016;6:81-88)

Key words: Excessive daytime sleepiness, Obstructive sleep apnoea syndrome, Epilepsy, Sleep disorders

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Introduction

The relationship between sleep and epilepsy has always been an object of study and, in patients with epilepsy, sleepiness is a frequently reported symptom. Indeed, sleep and epilepsy influence each other, and the comorbidity between sleep disorders and epilepsy is

frequently found in clinical practice.

Drowsiness, and sleep disorders in general, not only can alter the social and work activities in the general population, but - especially in patients with epilepsy - they may also result in deterioration of the natural history of the disease, increasing and facilitating the emergence of critical events, complicating and exacerbating the cognitive

and behavioural disorders.

Several studies have assessed the prevalence of excessive daytime sleepiness (EDS) in patients with epilepsy reporting conflicting data from 11% to 28%.^{1,2} More in detail, some studies have shown an increased prevalence of EDS and sleep disorders in patients with epilepsy comparing them to the general population.¹⁻⁶

In the literature, however, there are still discrepancies on the prevalence of specific sleep disorders such as OSAS, insomnia and RLS in patients with epilepsy.^{4,7-9} Insomnia is usually present in 30-40% of patients. While the frequency of OSAS ranges from 10% to 30%, and that of RLS from 10% to 33%.^{4,10,11} It is possible that the alterations between the different studies investigating sleep disorders in patients with epilepsy are partially related to biases in the selection of patients, but also to the use of different tests, different sample sizes as well as to differences in the type of treatment (mono-polytherapy).¹² In fact, many studies have focused their attention only on a population of patients with focal epilepsy undertaking a multidrug treatment. In this regard, it has long been known that the administration of antiepileptic drugs (AEDs), in particular those of the older generation, can facilitate the appearance of specific sleep disorders, such as OSAS for the action carried out on the centre of breath.

Therefore, it is not always easy to establish the causes of EDS in patients with epilepsy, whose genesis is undoubtedly multifactorial.^{2,12} In fact, many other factors can contribute such as undertaking a composite anti-epileptic therapy, the co-presence of other sleep disorders - obstructive sleep apnoea syndrome (OSAS) and the periodic leg movement during sleep (PLMs).^{1,13} and finally yet importantly, even the depression of mood.

Aims

The aim of our study was to assess the prevalence and characteristics of excessive daytime sleepiness (EDS) and certain sleep disorders (RLS, insomnia, OSAS) in a population of patients with epilepsy comparing it to a control population. In the study, other variables that can influence sleepiness or sleep disorders were also assessed; these variables are, for example, the depression of mood, the consumption of coffee and alcohol, smoking cigarettes, and the shift-work.

Methods

Step 1: Analysis of demographic and clinical characteristics of the study population

The study was performed through a prospective and consecutive recruitment of patients belonging to the centre for the diagnosis and treatment of epilepsy in the department of clinical neurosciences at the University of Palermo from January 2008 to July 2010.

We selected 99 patients with a confirmed diagnosis of epilepsy according to the criteria of the International League against Epilepsy (ILAE).

Patients older than 16 years, with sleep disorders not previously investigated, were included in the study. Clinical data including neurological examination, semiology of seizure, EEG and neuroimaging findings, and AEDs were documented.

Whereas, we excluded epileptic patients suffering from other neurological or psychiatric disorders, mental retardation, cardiopulmonary diseases or metabolic disorders (diabetes, liver failure, renal failure), patients with epilepsy receiving more than two antiepileptic drugs or a treatment with sedative-hypnotic, pregnant women, people with an age greater than 65 years.

The control group, matched by age (\pm 5 years), sex, and body mass index (BMI) to patients group, consisted of volunteers from among college students, relatives and friends of the medical staff. The same questionnaire form was given to them.

52 of our 99 patients with epilepsy were male with an average age of 36.07 (SD 13.49), a range from 17 to 64, and a BMI average of 26.2; 47 of them were female with an average age of 32.7 (SD 11.56), a range from 16 to 65, and a BMI average of 24.07 (Table 1).

All the selected patients had a positive diagnosis of epilepsy in accordance with the criteria of the last ILAE classification of 2010¹⁴ 61.6% had focal epilepsy and 38.3% a generalized one.

The control group consists of people without epilepsy and known sleep disorders.

The local ethics committee approved the study protocol and the patients gave their consent for the execution of the study.

Step 2: Giving questionnaires

Clinical aspects: after giving their consent for the study, all patients recruited were interviewed by a specialist neurologist, epileptologist, for the study of clinical, socio-demographic characteristics and the exposure to some risk factors such as smoking, coffee and alcohol. Clinical information obtained deals with the duration of the disease, the aetiology, the type and frequency of seizures, and the AED therapy taken. Afterwards, patients and controls were subjected to standardized and validated questionnaires for EDS and others sleep disorders.

Table 1. Demographic and clinical characteristics

Age (years)	34,48 (± 12,66)
BMI (kg/m ²)	25,15 (± 5,26)
Males (%)	52,5
Females (%)	47,4
Duration of epilepsy (years)	11,50 (± 10,52)
Age at epilepsy onset (years)	23,14 (± 12,64)
Generalized epilepsy (%)	38,3
Focal epilepsy (%)	61,6
- Symptomatic (%)	40,9
- Probably symptomatic (%)	57,3
Seizures during sleep (%)	51,5
One type of seizure (%)	74,7
- Generalized onset (%)	51,3
- Focal onset (%)	32,4
Drug resistance (%)	27,2
Therapy	
- Monotherapy (%)	68,6
- Bitherapy (%)	23,2
- Drug free (%)	8,08

BMI, body mass index.

We used a questionnaire form covers demographic data, medical problems and sleep habits. The answer also provide information on symptoms suggestive of EDS, insomnia, sleep apnoea and some movements disorders related to sleep.

We used the Italian version of Epworth Sleepiness Scale¹⁵ to determine EDS; it is based on eight questions related to the need to sleep in various life situation. Each question is rated on a 4-point scale ranging from 0 to 3, with a maximum score of 24 (cut-off of 10 is considered abnormal).

It was used the questionnaire of the Morfeo study¹⁶ to evaluate the subjective quality of nocturnal sleep. Patients were required to report the occurrence of sleep disturbances of the previous month. The cut-off to consider a response positive was three times or more a week. Using the replies to these five questions about sleep loss, various levels of insomnia classified as non-sleepless, sleepless level I and sleepless level II were established.

The Berlin questionnaire was employed to assess snoring and the risk of OSAS. Risk of apnoea was described by a positive score in, at least, two of the three categories in the questionnaire, including questions on snoring, apnoea, daytime sleepiness, hypertension and measurement of BMI. It was considered a high risk a positive score in two or more categories. Low risk: positive score in only one category or absence of any positive score in the three categories.¹⁷

Moreover others sleep disorders were included such as restless legs syndrome.

RLS complaints were defined according to the International

Restless Legs Syndrome study group criteria of Allen et al. in 2003. RLS was present if a "yes" response was given to the following: 1. Having unpleasant feelings in the legs like tingling, restless, frequently or almost every day. 2. It happens sometimes in one and sometimes in other legs. 3. Increasing during the evening. 4. Moving leads to partial relief. 5. This condition modifies sleeping.

Finally we used the Beck Scale for depression (Beck Depression Inventory II) to evaluate the simultaneous presence of mood disorders. Every heading includes four levels from 0 to 3. The score was calculated by adding the highest score under each seven heading consist of: sadness, pessimism, past failure, self-dislike, self-reproach, loss of interest and suicidal thoughts.

Instrumental aspects: the second phase of the study was conducted in collaboration with the IBIM, Institute of Biochemistry and Molecular Immunology Alberto Monroy of the National Council for Research of Palermo. We selected patients and controls to be monitored for sleep-disordered breathing based on the presence of at least one of the following three characteristics: 1) high risk of OSAS measured with the Berlin questionnaire, 2) excessive daytime sleepiness assessed by the ESS scale with a cut-off of 7, and 3) the presence of habitual snoring. Patients who fulfilled the inclusion criteria were 57. Among these, 43 (76%) gave their consent to execute the monitoring, 14 patients (25%) did not. According to the same criteria, 52 (65%) control subjects were chosen; among these, 34 were monitored and 18 (35%) did not give their consent to perform the examination.

The instrument used for the study of sleep is a portable device, named POLYMESAM (PM), a validated instrument in the detection of ventilatory disorders and in the diagnosis of obstructive sleep apnea syndrome (OSAS). The apnoea-hypopnoea index (AHI) was the standard applied to describe OSAS, and it was calculated by dividing the number of apnoeas and hypopnoeas on the total number of hours of sleep.

Simultaneously all subjects suspected for OSAS were studied by polysomnography (PSG) in a sleep laboratory. Then the diagnosis of OSAS was performed according to the official standards of the American Academy of Sleep Medicine Task Force.

Statistical analysis

Statistical analysis of the data obtained from this case-control study was performed comparing the continuous variables using T-test, and the categorical variables using χ^2 test. We have assessed

Table 2. Prevalence of EDS and some sleep disorders in patients with epilepsy compared to a group of healthy controls

	Patients(n:99)	Controls (n: 96)	p-value	Odds	95% CI	p-value
Mean ESS score	5,15 (0-21)	4,75 (0-14)	ns	1,0	0,9 -1,1	ns
EDS	11/99 (11,1%)	5/96 (5,20%)	ns	2,3	0,7 -6,8	ns
Shift work	5/99 (5,05%)	6/96 (6,25%)	ns	0,798	0,235-2,707	ns
Alcohol	21/99 (21,2%)	20/96 (20,2%)	ns	1,023	0,514-2,038	ns
Smoking	26/99 (26,2%)	22/96 (22,9%)	ns	1,198	0,623-2,303	ns
Coffee drinking	69/99 (69,6%)	72/96 (75%)	ns	0,767	0,408-1,440	ns
Depression	22/99 (22,2%)	5/96 (5,2%)	0,0006	5,200	1,880-14,383	0,001
Insomnia	51/99 (51,5%)	37/96 (38,5%)	ns	1,694	0,959-2,994	ns
RLS	13/99 (13,1%)	3/96 (3,1%)	0,01	4,686	1,291-17,010	0,022

CI, confidence interval; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness; RLS, Restless Legs Syndrome

the type of risk in patients with epilepsy compared to non epileptic ones, and the calculation of odds ratios and confidence intervals at 95%. The effect of demographic and epileptological variables on EDS and other sleep disorders was analysed through a univariate analysis (Student T-test for quantitative variables, χ^2 test for qualitative variables) and a multivariate one (logistic regression).

Results

1. Prevalence of EDS and some sleep disorders in patients with epilepsy compared to a group of controls

In the first part of our study, we evaluated the prevalence of excessive daytime sleepiness (EDS) and some sleep disorders in epileptic patients, comparing them to control subjects (Table 2).

Our results, confirmed by the univariate analysis, indicate greater daytime sleepiness (OR 2.3) and an increased risk of insomnia (OR 1.6) in patients with epilepsy compared to controls, even if values do not reach statistical significance.

Similarly - considering the frequency of probable risk factors such as shift-work, habit of cigarette smoking, coffee consumption, alcohol intake - there were no significant differences between cases and controls.

Instead, after seeking the presence of psychiatric disorders - mainly the depression of mood - in our two populations of patients with epilepsy and controls, there was a significantly higher frequency of the disorder in patients than in controls ($p = 0.0006$).

Likewise, it was established that the Restless Legs Syndrome (RLS) is significantly more frequent in patients with epilepsy than in controls (13.1% vs. 3.1%, $p = 0.01$). In particular, our data indicate that 46.1% of patients have a positive RLS and 53.8% a probable RLS. Moreover, linking this disorder to the type of epilepsy, it becomes ob-

Table 3. multivariate analysis of depression and RLS:two pathological conditions related to epilepsy

Multivariate analysis	Odds	95% CI	p-value
RLS	4,3	1,2-16,1	0,03
Depression	5,0	1,8-13,9	0,002

CI, confidence interval; RLS, Restless Legs Syndrome.

vious that RLS is present in 46.1% of cases with generalized epilepsy (in particular Janz Syndrome), and in 53.8% of cases with temporal focal epilepsy.

Even the univariate analysis confirms these results, with a significantly higher risk of RLS in epileptic patients than in controls (OR 4.6 $p = 0.022$), and with the appearance of mood disorders up to five times greater (OR 5.2 $p = 0.001$) compared to controls.

Finally, also the multivariate analysis - adjusted for the variables found significantly associated with epilepsy in the univariate analysis (RLS and depression) - shows that both depression and RLS are two pathological conditions closely related to epilepsy (Table 3).

2. Possible causes and clinical features of EDS in patients with epilepsy

We deepened the study investigating the possible causes of excessive daytime sleepiness in patients with epilepsy. For a descriptive analysis, significant differences between sleepy patients and non-sleepy were underlined considering the average age, significantly higher in sleepy people ($p = 0.002$), and a longer duration of disease ($p = 0.003$). Instead, for what concerns the type of epilepsy, there seems to be no correlation with sleepiness ($p = 0.03$). Just as there was no correlation found in our population of patients with epilepsy between insomnia and other variables analysed - demographic and epileptological ones (disease duration, age at onset of epilepsy, type of epilepsy or seizure type, drug resistance) - neither with possible risk factors (age, sex, BMI, alcohol consumption, smok-

ing, coffee) nor with sleep disorders as RLS.

A statistically significant association was obtained, however, between insomnia and other sleep disorders (OSAS) and between insomnia and the depression of mood. (Table 4).

3. Prevalence of OSAS in patients with epilepsy compared to controls

In the second part of the study, we evaluated the frequency of OSAS in our population of patients with epilepsy compared to controls.

Based on the inclusion criteria described above, 43 epileptic patients and 34 controls underwent a cardiorespiratory monitoring during night. There were no significant differences with regard to age ($t: 1.697, p = 0.0938$), sex (OR 0.825, $p = 0.907$, CI 0.301 to 2.258) and BMI ($t: 1.385, p = 0.1700$).

Similarly, there were no significant differences between cases and controls with regard to the frequency of the syndrome of obstructive sleep apnoeas. Once compared the average of AHI in controls to the one in the group of patients with epilepsy who tested positive for OSAS, it was clear that AHI is on average higher in patients with epilepsy, although it does not reach statistical significance.

An interesting fact to highlight is that among 19 patients with

OSAS only 10 (52.6%) were positive to the Berlin questionnaire. In the same way, among 14 positive controls for OSAS only 7 were positive to the Berlin questionnaire for a high risk of OSAS. This indicates that this questionnaire may, in some cases, underestimate the actual presence of OSAS (Table 5).

4. Clinical features of OSAS in patients with epilepsy

In order to clarify the characteristics of OSAS in our population of patients with epilepsy, we compared patients affected by OSAS undergoing cardiorespiratory monitoring to those unaffected.

In our population of patients with epilepsy, OSAS was significantly more frequent in males (89.4% vs. 43.75% $p = 0.0003$); it was related to a higher mean age ($p = 0.001$) and a higher BMI ($p = 0.004$). As regards the characteristics of the epileptic syndrome, OSAS is most often associated with a form of focal epilepsy ($p = 0.02$) and more frequently with secondarily generalized seizures ($p = 0.008$).

There seem to be, however, significant differences between OSAS and disease duration, nocturnal seizures, recurrent seizures, drug resistance or bitherapy.

All the variables, which were more frequently associated to OSAS in a descriptive analysis, were confirmed in a univariate one. In partic-

Table 4. Possible causes and clinical features of EDS in patients with epilepsy

Patients	EDS (n: 11)	without EDS (n: 88)	p -value	OR	p -value
Age (yrs)	45,1 (\pm 12,6)	33,1 (\pm 12,08)	0,002	1,1 (1,0-1,2)	0,006
BMI	26,45 (\pm 3,84)	24,99 (\pm 5,41)	ns	1,1 (0,9-1,2)	ns
Age at epilepsy onset	27,36 (\pm 18,42)	22,61 (\pm 11,7)	ns	1,0 (0,9-1,1)	ns
Duration of epilepsy	17,90 (\pm 15,88)	10,7 (\pm 9,48)	0,003	1,1 (1,0-1,2)	0,04
Males (%)	(72,7%) 8/11	(50 %) 44/88	ns	2,7 (0,7-10,7)	ns
Focal epilepsy (%)	(90,9%) 10/11	(57,9%) 51/88	0,03	7,2 (0,9-59,2)	ns
Seizures during sleep	(36,3%) 4/11	(53,4%) 47/88	ns	0,5 (0,1-1,8)	ns
Secondarily generalized seizures	(45,4%) 5/11	(46,5%) 41/88	ns	0,9 (0,3-3,4)	ns
Bitherapy	(27,2%) 3/11	(21,5%) 19/88	ns	1,4 (0,3-5,6)	ns
Drug-resistance	(36,3%) 4/11	(26,1%) 23/88	ns	1,6 (0,4-6,0)	ns
Depression	(54,5%) 6/11	(18,1%) 16/88	0,006	5,4 (1,5-19,9)	0,01
Imsonnia	(45,4%) 5/11	(52,2%) 46/88	ns	0,8 (0,2-2,7)	ns
RLS	(9,09%) 1/11	(13,6%) 12/88	ns	0,6 (0,1-5,4)	ns
OSAS	(45,4%) 5/11	(15,9) 14/88	0,002	4,4 (1,2-16,4)	0,03

EDS, excessive daytime sleepiness; OD, Odd ratio; BMI, Body Mass Index; RLS, Restless Legs Syndrome; OSAS, obstructive sleep apnoea syndrome.

Table 5. Prevalence of OSAS in patients with epilepsy compared to controls

	Patients (n:99)	Controls (n: 96)	p -value	Odds	95% CI	p -value
Risk of OSAS	17/99 (17,1%)	13/96 (13,5%)	ns	1,3	0,604-2,899	ns
OSAS	19/99 (19,1%)	14/96 (14,5%)	ns	1,4	0,6-3,0	ns
Moderate/Severe	12/99 (12,1%)	5/96 (5,2%)	ns	2,5	0,8-7,4	ns

CI, confidence interval; OSAS, obstructive sleep apnoea syndrome.

Table 6. Clinical features of OSAS in patients with epilepsy

	OSAS (n: 19)	no OSAS (n: 24)	p-value	OR	CI	p-value
Age	42,8 (±11,3)	34,7 (±11,24)	0,0239	1,1	(1,0-1,1)	0,03
BMI	28,2 (± 4,86)	27,88 (±5,46)	ns	1,0	(0,9-1,1)	ns
Age at epilepsy onset (yrs)	28,5 (± 16,5)	20,9 (±11,09)	ns	1,0	(0,9-1,0)	ns
Duration of epilepsy (yrs)	14,3 (±15,8)	14 (±10,3)	ns	1,0	(0,9-1,0)	ns
Males (%)	89,4% (17/19)	62,5% (15/24)	0,04	5,1	(0,9-27,4)	0,06
Focal epilepsy (%)	84,2% (16/19)	58,3% (14/24)	0,06	3,8	(0,9-16,7)	0,07
Seizures during sleep (%)	42,1% (8/19)	54,1% (13/24)	ns	0,6	(0,2-2,1)	ns
Secondarily generalized seizures (%)	73,6% (14/19)	37,5% (9/24)	0,02	4,7	(1,2-17,4)	0,02
Bitherapy	21% (4/19)	33,3% (8/24)	ns	0,5	(0,1-2,1)	ns
Drug-resistance	31,5% (6/19)	33,3% (8/24)	ns	0,9	(0,2-3,3)	ns

OSAS, obstructive sleep apnoea syndrome; OR, Odd ratio; CI, confidence interval; BMI, Body Mass Index.

ular, a high OR was found for the male sex, the type of focal epilepsy and PSG seizures. In the multivariate analysis adjusted for all the variables found significant in the univariate one - however - a later age of onset, male gender, BMI and PSG seizures turned out to be considerably related to OSAS (Table 6).

Discussion

The high incidence of excessive daytime sleepiness and sleep disorders in patients with epilepsy is well documented in the scientific literature.

Our study shows a higher frequency of *daytime sleepiness* in patients with epilepsy than in control subjects (11.1% vs. 5.20%). Our result is in accordance with some scientific works in which there is not a significant increase of sleepiness in epileptic patients compared to controls,^{1,2,4,5} although the data is still controversial.

Other authors, for example, report an increase of drowsiness or subjective disorders of sleep in patients with drug-resistant epilepsy compared to controls. However, we believe this result may be due to the selection of the study population undertaking a multidrug treatment and the use of different scales - not always validated - for the assessment of drowsiness.^{3,13,18}

In order to investigate the possible causes of excessive daytime sleepiness in patients with epilepsy, we assessed not only the raw data but also the simultaneous presence of psychiatric disorders, particularly the *depression of mood*. To this day, only one study in the literature demonstrated the association between daytime sleepiness and the depression of mood in a population of patients with epilepsy who took antiepileptic drugs and CNS sedative too.¹² Our study shows a high frequency of mood disorder in patients with epilepsy, who took only an antiepileptic therapy, reaching high statistical significance

when compared to controls ($p = 0.0006$).

In addition to psychiatric disorders, also *sleep disorders* - which often occur in comorbidity with epilepsy in clinical practice - have been little investigated by the literature so far. In our study, we explored clinically and by means of validated questionnaires: RLS, insomnia and presence of OSAS.

What emerges is a statistically significant association between *RLS and epilepsy* (13.1 vs. 3.1). Ours is, to our knowledge, one of the first studies in the literature showing this association. In particular, this was found both in patients with temporal lobe epilepsy (53.8% in our series), as previously described by de Weerd et al.,³ and in patients with generalized epilepsy (in particular with Janz syndrome (46.1% of patients). The last one represents, to our knowledge, a completely new data. Studies currently in the literature on the comorbidity between RLS and epilepsy are based mostly on case reports that consider only RLS symptoms^{1,4} and not the *RLS syndrome* on the basis of Allen diagnostic criteria. This finding is interesting for what concerns both the common pathogenetic mechanism between myoclonus of Janz syndrome and the PLM in the RLS, but it is also a suggestion to explore such symptomatology in clinical practice in more detail.

As regards *insomnia*, this was found in a high percentage of patients (51.5% vs. 38.5%) in our series, with a high risk in the univariate analysis although not related to the most severe forms of epilepsy.

This is in accordance with the few data in the literature reporting frequencies of insomnia similar to ours.^{4,11,19} After all, it is well known that there are several factors which can cause insomnia in patients with epilepsy: sleep fragmentation due to recurrent seizures, the effect of some AEDs, as well as the simultaneous presence of mood disorders.

Finally, another sleep disorder that we wanted to investigate is OSAS (*sleep apnoea syndrome*) - and which can aggravate the clinical picture of the patient with epilepsy interfering with control seizures, mood disorders, cognitive dysfunction, daytime sleepiness and quality of life.

In our study, once compared two populations subjected to offset printing, a higher prevalence of OSAS in patients than in controls was not observed (19.1% vs. 14.5%). Even though the data reported is not statistically significant, it is important to emphasize the selection performed on patients undergoing polygraph examination. In fact, we included, among patients and controls, those who had a high risk of OSAS in the Berlin questionnaire, and also those who had simple snoring or an increased score at ESS. This choice was motivated by the presence of patients in clinical practice who, despite having a negative Berlin questionnaire, showed a syndrome of obstructive sleep apnoea from an instrumental point of view.

In fact, from our data, it is clear that in about half the cases the Berlin questionnaire underestimates the frequency of OSAS, despite the use of a cut-off equal to 7 for the ESS (and not the standard cut-off of 10) as one of the inclusion criteria to perform offset printing. Indeed, this choice came from several evidences of the literature on limiting the usage of this scale in patients with epilepsy^{2,3,5,18,20} In one of his studies, Violani (2003) claims, for example, that - in the scale of ESS with a cut-off >10 - some conditions of intermediate somnolence are underestimated, which thus limits the accuracy of the test.

Indeed, in our sample, despite the fact that the population of patients with epilepsy had not been previously selected in terms of severity or refractory, the prevalence of OSAS was higher than in other studies.^{3,6,7} This discrepancy may be due in part to the different diagnostic methods used to screen sleep apnoeas, or even to different evaluation criteria.

Our results, however, might suggest that there are milder conditions of OSAS, perhaps asymptomatic ones, which - with less restrictive screening criteria as those used by us - can be stressed.

The association between OSAS and epilepsy has been a matter of debate, but their causal/effect relationship has not been clarified yet. In our study, OSAS is more common in male patients, the elderly ones, with a kind of focal epilepsy in accordance with the most recent literature.^{7,21} We also found a strong correlation between OSAS and PSG. It has been verified that hypoxemia related to apnoea may be associated with primarily or secondarily generalized crises. Finally, we found a greater frequency of moderate-severe forms of OSAS in

epileptics compared to controls, although this is not significant probably because of the low sample size. This could be explained by the fact that the two diseases affect each other and that the same focal epilepsy can favour an instability of sleep, facilitating the phases 1 and 2 of NREM sleep, during which the apnoeic event occurs more frequently.¹⁹⁻²³

In conclusions, our results, although they do not indicate a statistically significant prevalence of *EDS* in epileptic patients compared to controls, underline a completely new data in the literature: that is a close correlation between sleepiness and the depression of mood. Similarly, our study demonstrates the important association between epilepsy and sleep disorders, particularly with *Restless Legs Syndrome*. This outcome, in addition to having been little studied by the literature, is of particular importance since it allows improving the therapeutic approach of these patients, being the RLS a disorder treatable by a clinical point of view.

To conclude, our study confirms - as previously reported - that there are no statistically significant differences in the prevalence of OSAS among patients with epilepsy and controls, but it shows a higher percentage of OSAS in male patients, the elderly ones, with a severe form of focal epilepsy and secondarily generalized seizures.

In light of our results, it seems important to perform - in clinical practice and with epilepsy patients - a deepened ipnologic anamnesis aimed to investigate habits of sleep, sleep hygiene, presence of sleepiness and sleep disorders. In fact, the comorbidity between these ones and epilepsy, if recognized and treated early, can prevent misdiagnosis and improve the prognosis and the quality of life of patients.

References

1. Malow BA, Bowers RJ, Lin X. Predictor of sleepiness in epilepsy patients. *Sleep* 1997;20:1105-10.
2. Manni R, Tartara A. Evaluation of sleepiness in epilepsy. *Clin Neurophysiol* 2000;111(Suppl 2):S111-4.
3. de Weerd A, de Haas S, Otte A, et al. Subjective sleep disturbance in patients with partial epilepsy: a questionnaire-based study on prevalence and impact on quality of life. *Epilepsia* 2004;45:1397-404.
4. Khatami R, Zutter D, Siegel A, Mathis J, Donati F, Bassetti C. Sleep-wake habits and disorders in a series of 100 adult epilepsy patients- a prospective study. *Seizure* 2006;15:299-306.
5. Vignatelli L, Bisulli F, Naldi I, et al. Excessive Daytime Sleepiness and subjective sleep quality in patients with nocturnal frontal lobe epilepsy: a case control study. *Epilepsia* 2006;47(Suppl 5):73-7.
6. Al-Abri M, Al-Asmi A, Al-Shukairi A, et al. Frequency of obstructive

- sleep apnea syndrome among patients with epilepsy attending a tertiary neurology clinic. *Oman Med J* 2015;30:31-5.
7. Manni R, Terzaghi M, Arbasino C, Sartori I, Galimberti CA, Tartara A. Obstructive sleep apnea in a clinical series of adult epilepsy patients: frequency and features of the comorbidity. *Epilepsia* 2003;44:836-40.
 8. Weathervax KJ, Lin X, Marzec ML, Malow BA. Obstructive sleep apnea in epilepsy patients: the sleep apnea scale of the sleep disorders questionnaire (SA-SDQ) is a useful screening instrument for obstructive sleep apnea in a disease-specific population. *Sleep* 2003;4:517-21.
 9. Sonka K, Juklickova M, Pretl M, Dostalova S, Horinek D, Nevsimalova S. Seizures in sleep apnea patients: occurrence and time distribution. *Sb Lek* 2000;101:229-32.
 10. Manni R, Terzaghi M. Comorbidity between epilepsy and sleep disorders. *Epilepsy Res* 2010;90:171-7.
 11. Grigg-Damberger MM, Ralls F. Sleep disorders in adults with epilepsy: past, present, and future directions. *Curr Opin Pulm Med* 2014;20:542-9.
 12. Jenssen S, Gracely E, Mahmood T, Tracy JI, Sperling MR. Subjective somnolence relates mainly to depression among patients in a patients tertiary care epilepsy center. *Epilepsy Behav* 2006;9:632-5.
 13. Malow BA, Levy K, Maturen K, Bowes R. Obstructive sleep apnea is common in medically refractory epilepsy patients. *Neurology* 2000;55:1002-7.
 14. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010;51:676-85.
 15. Vignatelli L, Plazzi G, Barbato A, et al. Italian version of the Epworth sleepiness scale: external validity. *Neurol Sci* 2003;23:295-300.
 16. Terzano MG, Parrino L, Cirignotta F, et al. Studio Morfeo: insomnia in primary care, a survey conducted of Italian population. *Sleep Med* 2004;5:67-75.
 17. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 1999;131:485-91.
 18. Vaughn BV, Miller MT, D'Cruz OF, Messenheimer J. Prevalence of sleep complaints in patients with epilepsy: application of the Epworth sleepiness scale. *Sleep Res* 1996;25:453.
 19. Manni R, Terzaghi M. Comorbidity between epilepsy and sleep disorders. *Epilepsy Res* 2010;90:171-7.
 20. Cluydts R, De Valch E, Verstraeten E, Theys P. Daytime sleepiness and its evaluation. *Sleep Med Rev* 2002;6:83-96.
 21. Yildiz FG, Tezer FI, Saygi S. Temporal lobe epilepsy is a predisposing factor for sleep apnea: A questionnaire study in video-EEG monitoring unit. *Epilepsy Behav* 2015;48:1-3.
 22. Terzaghi M, Ghiotto N, Sances G, Rustioni V, Nappi G, Manni R. Episodic cluster headache: NREM prevalence of nocturnal attacks. Time to look beyond macrostructural analysis? *Headache* 2010;50:1050-4.
 23. Derry CP, Duncan S. Sleep and epilepsy. *Epilepsy Behav* 2013;26:394-404.