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Parasomnias, sleep-related movement disorders and physiological sleep variants in epilepsy: a reciprocal relationship?

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Summary

Abstract

Purpose: The link existing between epilepsy and sleep is widely recognized. In particular, in Idiopathic Generalized Epilepsies (IGE), a close link of seizures to the sleep–wake cycle has been demonstrated. However, little is known about the prevalence and the clinical consequences of the comorbidity between focal and generalized epilepsy and sleep disorders, especially those sleep phenomena classified as isolated symptoms or normal variants. Objective of the study was to evaluate the frequency of sleep disorders and physiological sleep variants in a group of adult patients with focal and generalized epilepsy as compared to healthy controls by means of nocturnal polysomnography.

Methods: We performed a retrospective observational study in the Neurological Clinic of the University of Catania. We studied patients with diagnosis of focal epilepsy, IGE and controls without epilepsy who underwent a polysomnography in the 2015-2019 period. Exclusion criteria were: obstructive sleep apnoea syndrome and epileptic encephalopathy. The following sleep disorders were considered: NREM-related parasomnias; REM-related parasomnias; sleep-related movement disorders; isolated symptoms or normal variants.

Results: *Focal epilepsy*: 100 patients (mean age 30.3 ± 14.7 years, 40 [40%] men) and 62 controls (mean age 36.4 ± 15.9 years, 20 [32.2%] men) were studied. A significant higher percentage of sleep disorders was recorded in patients as

compared to controls (73% vs 48.4%; p=0.002). In particular, we found a higher frequency of periodic limb movements (PLM) (20% vs 4.8%; p=0.007), bruxism (20% vs 4.8%; p=0.007) and neck myoclonus (22% vs 4.8%; p=0.003). *Idiopathic Generalized Epilepsy*: 35 patients with IGE (mean age 28.8 ± 13.1 years, 11 [31.4%] men) and 56 controls without epilepsy (mean age 32.8 ± 11.5 years, 18 [32.1%] men) were studied. A significant higher percentage of sleep disorders was found in patients (82.9% vs 50%, p=0.002) compared to controls. In particular, we found a higher frequency of disorders of arousal (60% vs 30.3%; p=0.01), bruxism (28.6% vs 5.4%; p<0.01) and neck myoclonus (25.7% vs 5.4%; p<0.01).

Conclusion: Our study demonstrated a high frequency of sleep disorders in patients with both focal and generalized epilepsy. Although it can be due to different underlying physiopathological mechanisms, this comorbidity should be taken into account in order to ensure an optimal seizures control in these patients.

1. General Introduction

1.1 Epilepsy and sleep

Sleep and epilepsy are two bidirectionally interconnected phenomena [1]. The close link existing between epilepsy and sleep is well known since the times of Hippocrates [2]. Since then, the activating function of sleep on epilepsy has been widely recognized as well as the effect of epilepsy on sleep [3].

The influence of sleep on epilepsy is supported by the observations that, in many epileptic syndromes, seizures and interictal discharges are more frequent during sleep [4,5].

The reasons for this close relationship have to be found in the corticothalamic system, the main structure responsible for generating sleep oscillations. In particular, spike-wave discharges can be easily generated in the cortex, especially during NREM sleep, as a result of increasing synchrony and oscillation within cortical networks, typical of these phases of sleep, which normally generate sleep spindles and high amplitude delta waves. On the other hand, during REM sleep, asynchronous discharge patterns generate divergent synaptic signals making it less likely for epileptic activity to propagate [6]. Indeed, epileptiform discharges in patients with epilepsy are seen more frequently during the deeper stages of NREM sleep, while although less frequent, interictal epileptiform discharges

occurring during REM sleep can be more accurate for a definitive localization of epilepsy focus [3].

As regard to seizures, some epilepsy syndromes are known to have close relationships with sleep state, with seizures typically occurring exclusively or predominantly during sleep or at awakening [3]. These syndromes are defined as Sleep-Related Epilepsies (SRE) and they are classified in three distinctive phenotypes: sleep-associated epilepsies, sleep-accentuated epilepsies and awakening epilepsies [7]. In these syndromes, sleep exerts a facilitating function on seizures, but also influences the chance of seizures propagation, with a higher likelihood of occurrence of tonic-clonic seizures during sleep or immediately after awakening as is the case for both focal epilepsies, such as temporal lobe epilepsy (TLE), and generalized syndromes, such as Juvenile Myoclonic Epilepsy (JME) [3].

On the other hand *the influence of epilepsy on sleep* is demonstrated by different studies showing that sleep disorders are two to three times more common in adults and children with epilepsy compared with age-matched controls [8]. In particular, patients with epilepsy often complain of excessive daytime sleepiness (EDS) and the causes may include nocturnal seizures, sedative effects of antiseizure medications (ASMs), poor sleep hygiene and co-morbid primary sleep disorders [1]. Indeed, interictal epileptiform discharges and seizures themselves may interrupt sleep continuity, leading to poorly restorative sleep and

EDS. Therefore, it can be hypothesized that, since seizures can affect sleep, use of ASMs may improve sleep quality through improved seizure control. However, all of the older and some newer ASMs have important modulatory effects on sleep physiology, with a possible negative effect on sleep stability [1,9]. Hence, also the effects of epilepsy treatments on sleep architecture have to be considered to optimize the management of patients with epilepsy.

For all the above-mentioned reasons, the relationship between *sleep and epilepsy* can be considered as a particularly vicious cycle with reciprocal detrimental influences: thus the definition of "unfortunate bedfellows" [10] (Figure 1).

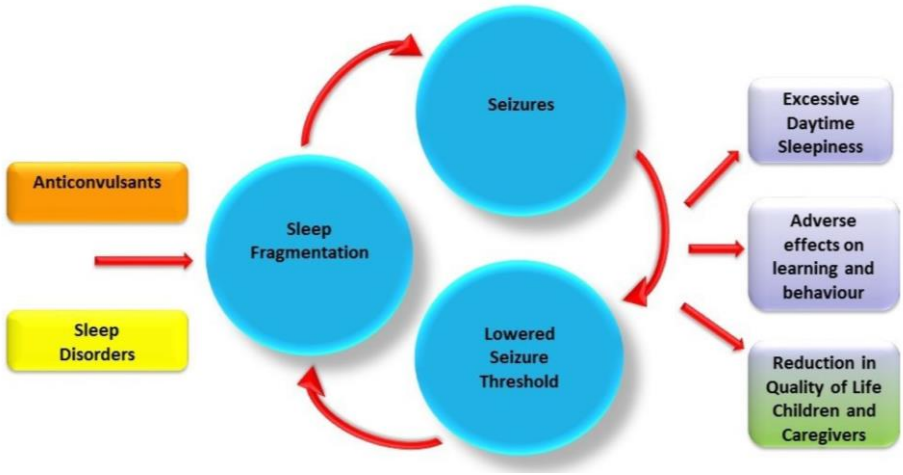

Figure 1: Reciprocal relationships between sleep and epilepsy (*From Gibbon et al. Arch Dis Child 2018*).

1.2 Focal epilepsy and sleep

Patients with focal epilepsy have been shown to frequently manifest sleep complaints. Indeed, among focal epilepsies, temporal lobe epilepsy (TLE) has been found to be more related with sleep changes showing an alteration of sleep architecture with reduced sleep efficiency and greater sleep fragmentation [11], even on nights without any seizure. Therefore, it seems that the presence of epilepsy itself predisposes to sleep disruption. The effects of temporal lobe seizures on sleep structure are characterized by a significant decrease in REM the following night after a seizure with increase of the lighter stages of sleep such as N1 and decreased sleep efficiency [12,13]. Moreover, temporal lobe seizures tend to generalize more frequently during sleep [14]. Even if uncommon, a nosological entity called "nocturnal temporal lobe epilepsy" has been described with seizures occurring predominantly during night sleep [15]. On the other hand, the occurrence of minor motor events (MMEs) during sleep in TLE has been well characterized with a study demonstrating the presence of stereotyped nocturnal motor events significantly more frequent in patients with mesial TLE than in healthy controls. In particular, a higher frequency of oroalimentary automatisms, limb dystonia, gestural automatisms, and straightening movements in this group of patients has been found and they were associated with the presence of epileptiform EEG abnormalities [16] (Figure 2).

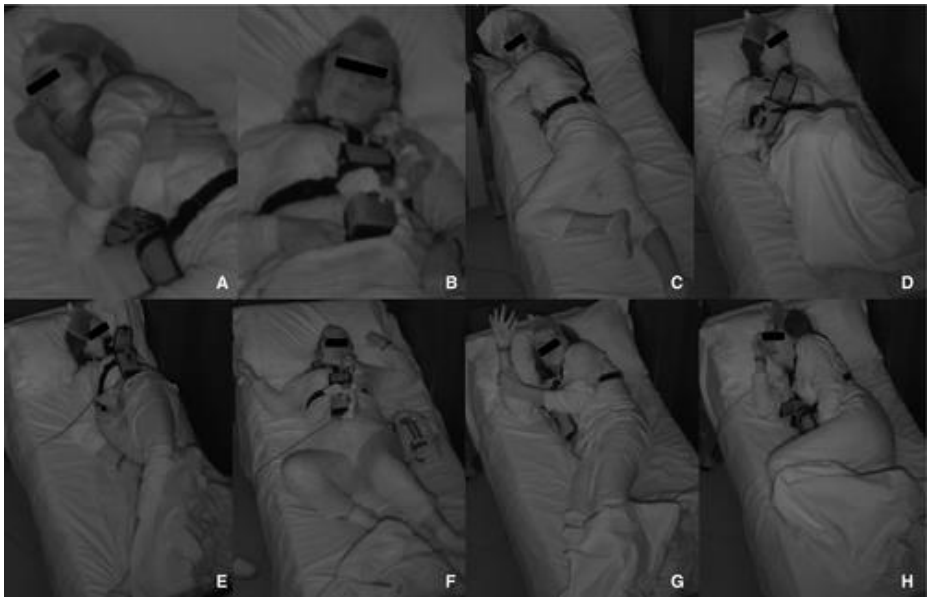

Figure 2: Minor motor events in sleep in temporal lobe epilepsy (*From Giuliano et al. Epilepsia 2017*).

Patients with frontal lobe epilepsy (FLE) seem to show a higher tendency to manifest seizures during sleep [11], with some patients manifesting seizure exclusively during sleep [14]. Moreover, sleep architecture has been found to be altered also in these patients with increased wakefulness after sleep onset, increased REM latency, and increased slow-wave sleep and reduced REM sleep as compared to controls [17].

Sleep-related hypermotor epilepsy (SHE) can be considered one of the most peculiar examples of SRE since the typical hypermotor seizures occur, in the majority of cases, during nigh-time sleep, with most of seizures usually occurring during N3 deep sleep [17,18]. Significant polysomnographic alterations have

been found also in patients with SHE in terms of both macro and microstructural parameters. In terms of sleep macrostructure, SHE patients show a significant increase in wake after sleep onset, N3 sleep duration, sleep and REM latencies, with a decrease in REM sleep duration and sleep efficiency [17,18]. Regarding sleep microstructure, patients with SHE present a significant increase of cyclic alternating pattern (CAP) time and CAP rate with an enhancement of the A phases of CAP [17].

Finally, among focal epilepsies, are classified as SRE two idiopathic self-limited syndromes such as epilepsy with centro-temporal spikes (ECTS) and Panayiotopoulos syndrome (PS), both with seizures occurring mainly during NREM sleep [7].

Even if classified as epileptic encephalopathies, other SRE that should be mentioned are: electrical status epilepticus in sleep (ESES), a developmental epileptic encephalopathy with a characteristic EEG activation in sleep, especially throughout NREM sleep; Landau–Kleffner syndrome (LKS) a subtype of ESES with spike and waves during NREM sleep associated with acquired epileptic aphasia; West syndrome (WS), an epileptic encephalopathy with epileptic spasms occuring in clusters shortly after awakening; and Lennox–Gastaut syndrome (LGS), a severe epileptic and developmental encephalopathy with tonic seizures during NREM sleep [7].

1.3 Generalized epilepsy and sleep

The research has frequently focused on the sleep alterations of Genetic Generalized Epilepsies (GGE), and in particular in Juvenile Myoclonic Epilepsy (JME), for which a close link to the sleep–wake cycle has been demonstrated [19–21].

In Idiopathic Generalized Epilepsies (IGE) recently renamed as Genetic Generalized Epilepsies (GGE) [22] abnormalities in sleep architecture have been found [23] raising the possibility that epileptiform discharges may disrupt the quality of sleep leading to a chronically aroused state [24]. In particular, a reduction in slow-wave sleep and increased REM latency have been described [14]. Moreover, reduced sleep quality and excessive daytime sleepiness have been reported in patients with IGE through questionnaires [25] possibly leading to an increased risk of seizure recurrence despite an appropriate pharmacological treatment. For this reason, sleep disorders should be taken into consideration for the therapeutic management of patients with IGE. [26].

Among IGE, in particular, JME has a complex relationship with sleep, the latter affecting the former and vice versa. Moreover, the electro-clinical manifestations of JME have a close relationship to the sleep–wake cycle [19,20,27–29] since myoclonic jerks in the early morning shortly after awakening are one of the

hallmarks of the syndrome [21]. Macrostructural analysis in patients with JME showed a slight predominance of EEG epileptiform activity during slow wave sleep [25] with the consequence of macrostructural and microstructural sleep alterations such as decreased sleep efficiency, prolonged sleep latency, decreased percentage of N2 sleep and total NREM sleep, prolonged REM latency, decreased REM percentage, increased wakefulness after sleep onset and higher CAP rate than healthy controls [21]. Moreover, various sleep disorders have been described in patients with JME including insomnia, obstructive sleep apnea syndrome, narcolepsy, periodic limb movements, and parasomnias, but the majority of the studies exploring these comorbidities were based on questionnaires rather that an objective evaluation through polysomnographic recordings [21]. It has been demonstrated that reduced sleep quality and daytime sleepiness in patients with JME increase the risk of seizure occurrence in spite of an appropriate pharmacological treatment, especially in younger patients [26].

Another IGE classified among SRE, as awakening epilepsy, is epilepsy with generalized tonic-clonic seizures alone (GTCS-a) since it is characterized by GTCS that typically occur shortly after awakening from night or daytime sleep. As in JME, seizures are precipitated by sleep deprivation and forced early awakening, while interictal discharges are activated by NREM sleep [7].

Regarding Childhood Absence Epilepsy (CAE), although the clinical manifestations and EEG abnormalities are typically seen during wakefulness,

sleep seems to exacerbate the development of the pathological EEG activity. In particular, during NREM sleep, there is an activation of the spike and wave discharges, shorter and fragmented as compared to wake state, while during REM sleep the EEG abnormalities are less frequent but with a morphology similar to that of wakefulness [4]. Regarding sleep macrostructure in CAE patients, an increase in sleep latency, REM latency, number of arousals, wake after sleep onset [4,5] and stage 1 and a decrease of REM, slow wave sleep and total sleep time have been described [30]. It has been demonstrated that control of absences and EEG normalization in drug-naïve CAE patients are accompanied by more continuous, stable and efficacious sleep [30].

Less is known about the link existing between sleep and other forms of IGE such as Juvenile Absence Epilepsy (JAE) or Eyelid Myoclonia with Absences (EMA), for which few studies until now have focused on their characteristics during sleep nor on the possible comorbidity with sleep disorders.

1.4 Epilepsy and sleep disorders

Sleep disorders are widely common in the general population but they are significantly more prevalent in people with epilepsy [8,31]. Indeed, self-reported sleep disturbances are twice as prevalent in people with epilepsy as compared to healthy controls with a significant impairment of quality of life [32]. Symptoms

of disturbed sleep in patients with epilepsy can be often overlooked, however they are frequent and can contribute to the poor outcome of epilepsy itself [33].

The majority of studies exploring the comorbidity between epilepsy and sleep disorders are mainly based on the clinical history through structured interviews and validated questionnaires [31,32,34]. Only a few studies explored through video-polysomnography the frequency of sleep disorders in patients with epilepsy mainly focusing on sleep apnoea and on sleep correlates of restless legs syndrome (RLS) [32].

The most convincing evidence up to now of the comorbidity between epilepsy and sleep disorders is about obstructive sleep apnoea syndrome (OSAS) which seems to coexist with epilepsy in about 10% of adult patients with epilepsy and up to 30% of drug resistant subjects [32,35]. It has been also demonstrated that treatment of OSAS significantly improves seizure control in people with epilepsy [32].

As regard to RLS, however, a good estimate on the prevalence of this disease and the comorbid periodic limb movements in sleep (PLMs) in people with epilepsy cannot be made based on literature evidences, which have given until now conflicting results [32].

Evidences are scarce as regard to sleep-related movement disorders other than RLS or PLM and epilepsy.

Sleep-related bruxism has been rarely evaluated in epilepsy with findings showing an equal or lower prevalence than the general population [36,37].

On the other hand, other sleep-related movement disorders such as sleep-related rhythmic movement disorders or benign sleep myoclonus in infancy are typical of the childhood, not being present in adult subjects [38]. Finally, propriospinal myoclonus at sleep onset is a rare, controversial, hyperkinetic movement disorder occurring mainly during sleep, involving the axial muscles [39,40]. Up to now, only a few cases have been described [40–43]. Moreover, recently the voluntary rather than pathological nature of propriospinal myoclonus has been debated [44,45], therefore it cannot be ruled out that propriospinal myoclonus at sleep onset might have a psychogenic origin.

Moreover, while there is some literature about the coexistence of sleep disorders, and in particular NREM parasomnias and epilepsy in children [32,46], data regarding NREM and REM parasomnias or sleep-related movement disorder and epilepsy are scarce in adult patients [32,47].

Different studies found an increased prevalence of NREM parasomnias also called disorders of arousals (DoA) in patients with epilepsy. In fact DoA have been proven to be more frequent in mesial TLE and in SHE [8,31,48]. In particular SHE and DoA have always been two strictly related nosological entities because of the similarities between the behavioral patterns found in these two disorders [49,50]. The higher prevalence of DoA among patients with SHE

has been partially explained by various hypotheses such as a common genetic predisposition for both seizures and arousal disorders or a shared pathophysiologic mechanism that involves an abnormal arousal system in these patients. All the previous evidences confirm that SHE is characterized by a distinctive sleep pattern mainly represented by NREM sleep instability, more prevalent during N3 deep sleep [51,52]. This can be linked to the presence of interictal epileptiform discharges and seizures that are typically more common during this phase of sleep [53].

There are some evidences demonstrating that REM sleep behavior disorder (RBD) might be more frequent in elderly people with epilepsy [47] than in general population. Nonetheless both disorders could co-occur by chance in the elderly, as both conditions are more frequent in older age.

At any rate, in contrast with all the other evidences, the study by Unterberger et al. demonstrated that chronic sleep disturbances are not increased in patients with well-controlled epilepsy without relevant comorbidities, suggesting that comorbidities and insufficient seizure control are the major contributors of sleep disturbance in epilepsy [34]. Therefore the results of this study raised the question whether "abnormal sleep in patients with epilepsy is due to epilepsy per se or we should have a more holistic view" [54].

1.5 Epilepsy and isolated symptoms and normal variants

Aside from the nosological entities classified as sleep disorders according to the International Classification of Sleep Disorders (ICSD third edition) [55], a group of manifestations exist for all categories of sleep disturbances, classified as "isolated symptoms and normal variants" [55]. This group consists of clinical manifestations occurring during sleep that are borderline abnormal but not otherwise specific disorders. For example, for sleep-related breathing disorders, snoring and catathrenia are classified as normal variants; among parasomnias, sleep-talking; and among sleep related movement disorders excessive fragmentary myoclonus, sleep starts and high frequency leg movements such as alternating leg muscle activation (ALMA) [55].

One recently described sleep-related manifestation, which is still not part of the ICSD is neck myoclonus, initially described as a physiological phenomenon [56], present among other non-pathological motor events during healthy sleep [57].

Up to now there are no studies in literature exploring the possible association of these phenomena with epilepsy.

1.6 Objective

Objective of the present study was to evaluate the frequency of sleep disorders and physiological sleep variants in a group of adult patients with epilepsy as compared to controls without epilepsy, by means of nocturnal polysomnography.

In particular, we aimed at evaluating the frequency of sleep disorders and physiological sleep variants:

- in a group of adult patients with focal epilepsy as compared to healthy controls without epilepsy;
- in a group of adult patients with Idiopathic Generalized Epilepsy as compared to healthy controls without epilepsy.

2. Materials and methods

2.1 Study population: Focal epilepsy and controls

We performed a retrospective observational study at the Neurological Clinic of the University of Catania. All patients with a diagnosis of focal epilepsy [58], who underwent a nocturnal video-polysomnography in the 2015-2019 period were considered for the study. Nocturnal video-polysomnography (PSG) was routinely performed as part of the standard diagnostic procedures. Patients underwent neurological examination, a standard EEG recording and conventional structural MRI. Exclusion criteria were the presence of an epileptic encephalopathy and the diagnosis of obstructive sleep apnoea syndrome.

Controls without epilepsy were selected among subjects who underwent a polysomnographic recording in the same study period for episodes of loss of consciousness and for whom a diagnosis of epilepsy or any other neurological

disease, following accurate diagnostic procedures, has been excluded. Subjects with diagnosis of obstructive sleep apnoea syndrome have been excluded as well. Subjects who had undergone PSG for any sleep complaint were excluded.

2.2 Study population: Idiopathic Generalized Epilepsy and controls

All patients with a diagnosis of IGE [58,59], who underwent a nocturnal polysomnography in the 2018-2019 period were enrolled in the study. Based on clinical features, patients were classified in five IGE subtypes; JME [60], JAE and GTCSA according to the most recent classification. Moreover, diagnosis of EMA was made according to the following clinical criteria: frequent occurrence of eyelid myoclonia with or without brief absences; generalized epileptiform activity (>3 Hz spike and wave/polyspike and wave or >3 Hz polyspike discharges) triggered by eye closure; generalized photoparoxysmal EEG response or a history of visually induced seizures [61–63].

Patients underwent neurological examination, a standard EEG recording and conventional structural MRI. Exclusion criteria were: the presence of an epileptic encephalopathy and the diagnosis of obstructive sleep apnoea syndrome.

Controls without epilepsy were selected among subjects who underwent a polysomnographic recording in the same study period for episodes of loss of consciousness and for whom a diagnosis of epilepsy or any other neurological

disease, following accurate diagnostic procedures, has been excluded. Subjects with diagnosis of OSAS have been excluded as well. Subjects who had undergone PSG for any sleep complaint were excluded. All patients with IGE and controls were adults of less than 65 years of age.

2.3 Clinical variables

All the clinical data of patients were retrospectively extracted by their medical records. The following clinical variables were taken into account for patients with focal epilepsy: sex, age, lobe of origin, etiology according to the most recent classification [58], age of onset of epilepsy, clinical reports of seizures during sleep, comorbidities, presence of cognitive deficits, use ASMs, antidepressants or benzodiazepines and drug resistance.

The following clinical variables were taken into account for patients with IGE: sex, age, family history for epilepsy, age of onset of epilepsy, comorbidities, presence of cognitive deficits, disease duration, use and type of ASMs and drug resistance. Also, antidepressants or benzodiazepines use was considered. Moreover, the seizure types (absences, limbs myoclonia, eyelid myoclonia, generalized tonic clonic seizures) ever manifested by the patients during the disease course and at the last follow-up visit were taken into account, as well as the presence of photosensitivity and eye closure sensitivity. Finally, the presence

of seizure-freedom at the last follow-up was evaluated as the absence of any type of seizure (absences, myoclonia or GTCS) for at least two years at the last follow-up visit.

For both epilepsy groups drug resistance was defined as the persistence of seizures despite two ASMs given at an adequate dosage [64] which was evaluated by reviewing medical records of the last follow-up visits in our center for each patient.

For the control group the following variables were analysed: sex, age, comorbidities, use of drugs such as ASMs, antidepressants or benzodiazepines.

2.4 Polysomnographic recordings

All patients and controls underwent an overnight video-polysomnography (VPSG), performed according to the American Association of Sleep Medicine guidelines [65]. All the sleep recordings were reviewed by a board-certified sleep expert (LG). All the subjects spent a previous night in the ward in order to avoid the first night effect. The PSG recording was carried out using a minimum of eight-channel EEG, placed according to the International 10-20 system, two electrocardiographic derivations, chin and right and left anterior tibialis electromyography (EMG) electrodes, electro-oculogram. Nasal thermistor, snore

monitor, chest and abdominal movements, pulse rate and oximetry have been used.

The following polysomnographic macrostructural parameters were assessed: total sleep time (TST); sleep efficiency (SE); sleep latency (SL); time spent in nocturnal wakefulness (WASO); percentage of NREM (N1, N2, N3) and REM sleep stages.

The following sleep disorders were taken into account: NREM-related parasomnias such as disorders of arousal (DoA) from NREM [66]; REM-related parasomnias such as REM sleep behaviour disorder (RBD) [65]; sleep-related movement disorders such as periodic limb movements in sleep (PLMs) [65] and bruxism [65]; isolated symptoms or normal variants such as alternating leg muscle activation (ALMA) [65,67], excessive fragmentary myoclonus (EFM) [65], and neck myoclonus (NM) [56].

The diagnosis of the above-mentioned sleep disorders was made according to the International Classification of Sleep Disorders (ICSD third edition) [55].

In particular, a DoA was defined as the presence of a dissociation EEG pattern characterized by an α rhythm in posterior channels, and an anterior and midline theta-delta activity, associated with muscular artifact or a video event of complex motor behavior [66] (Figure 3).

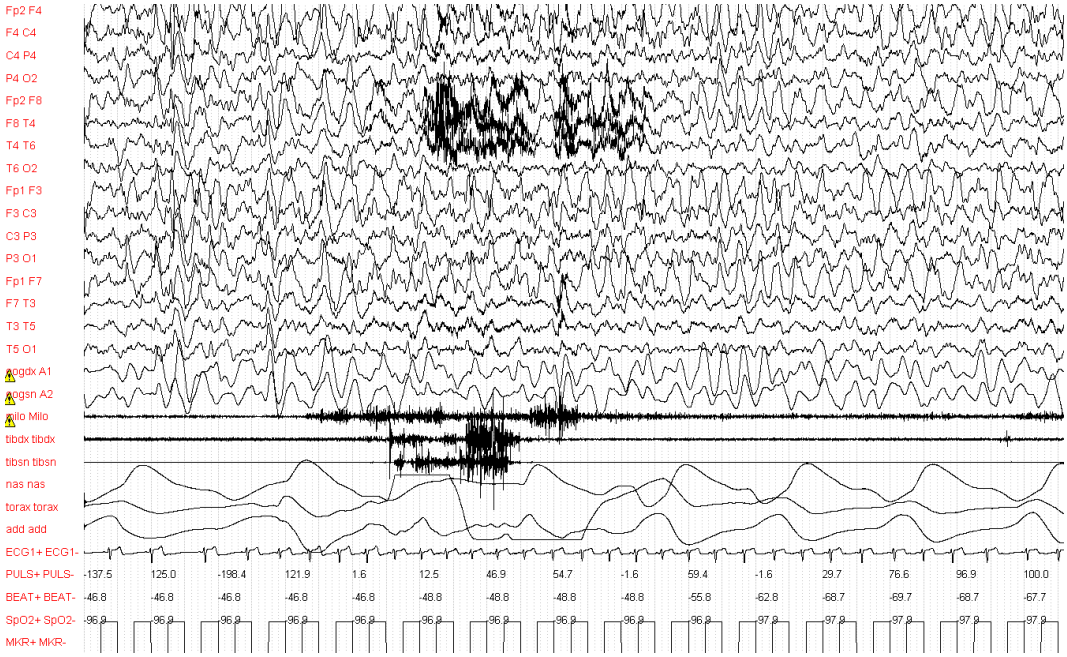

Figure 3: Epoch of N3 sleep showing a disorder of arousal (DoA) from NREM sleep.

First 16 derivations, right and left electroencephalogram (EEG) derivations in a bipolar montage; eogdx, right electrooculogram; eogsn, left electrooculogram; milo, chin EMG channel; tibdx, right anterior tibialis; tibsn, left anterior tibialis; nas, oronasal airflow; torax, thoracic movements; add, abdominal movements; ECG, electrocardiographic derivations; PULS pulse oximetry signal; BEAT, heart frequency; SpO2, oxygen saturation.

RBD was represented by episodes of behavior or vocalization documented by PSG to arise from REM sleep with evidence of REM sleep without atonia on PSG [55] (Figure 4).

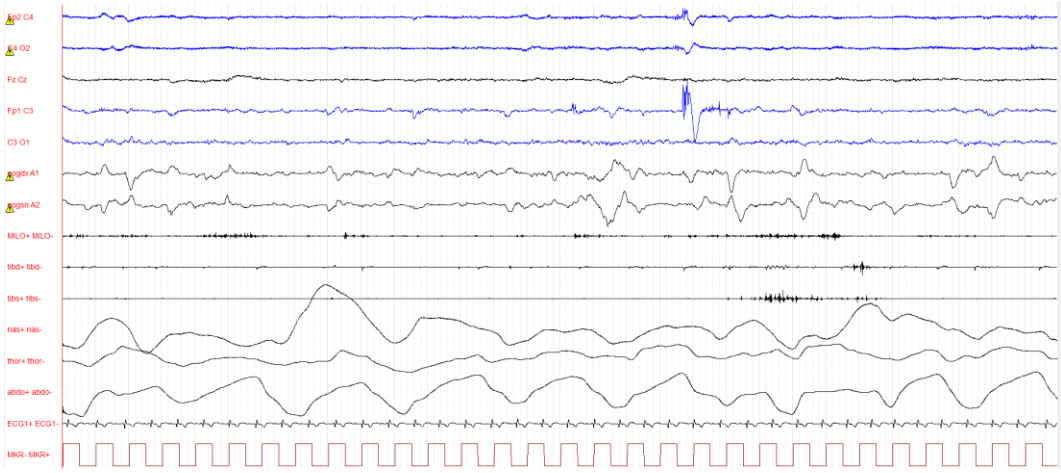

Figure 4: Epoch of REM sleep showing an episode of Rem Behavior Disorder (RBD).

First 5 derivations, right and left electroencephalogram (EEG) derivations in a bipolar montage; eogdx, right electrooculogram; eogsn, left electrooculogram; milo, chin EMG channel; tibdx, right anterior tibialis; tibsn, left anterior tibialis; nas, oronasal airflow; torax, thoracic movements; add, abdominal movements; ECG, electrocardiographic derivations.

PLMs were considered as periodic limb movements lasting 0.5 to 5 seconds, occurring 5 to 90 seconds of each other, with at least four of these movements appearing in a series. PLMs was diagnosed when the frequency of typical periodic limb movements was ≥15/h [55] (Figure 5).

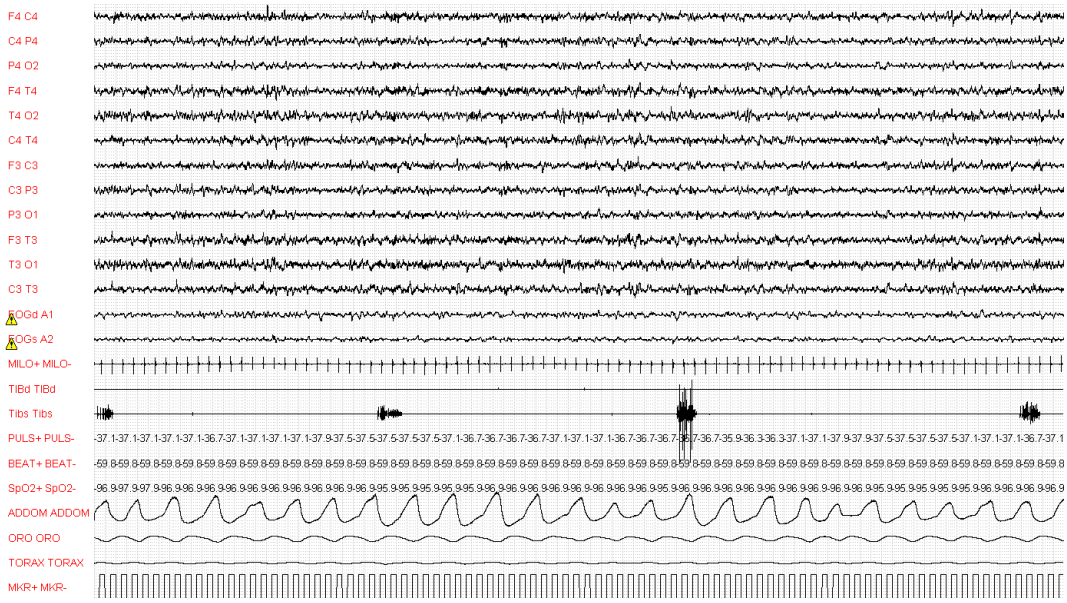

Figure 5: Epoch of N2 sleep showing periodic limb movements in sleep (PLM). First 12 derivations, right and left electroencephalogram (EEG) derivations in a bipolar montage; eogdx, right electrooculogram; eogsn, left electrooculogram; milo, chin EMG channel; tibdx, right anterior tibialis; tibsn, left anterior tibialis; oro, oronasal airflow; torax, thoracic movements; addom, abdominal movements; PULS pulse oximetry signal; BEAT, heart frequency; SpO2, oxygen saturation.

Sleep-related bruxism was considered as brief or sustained elevations of chin EMG activity that are at least twice the amplitude of background EMG, of at least 0.25 seconds in duration, occurring in sequences [65] (Figure 6).

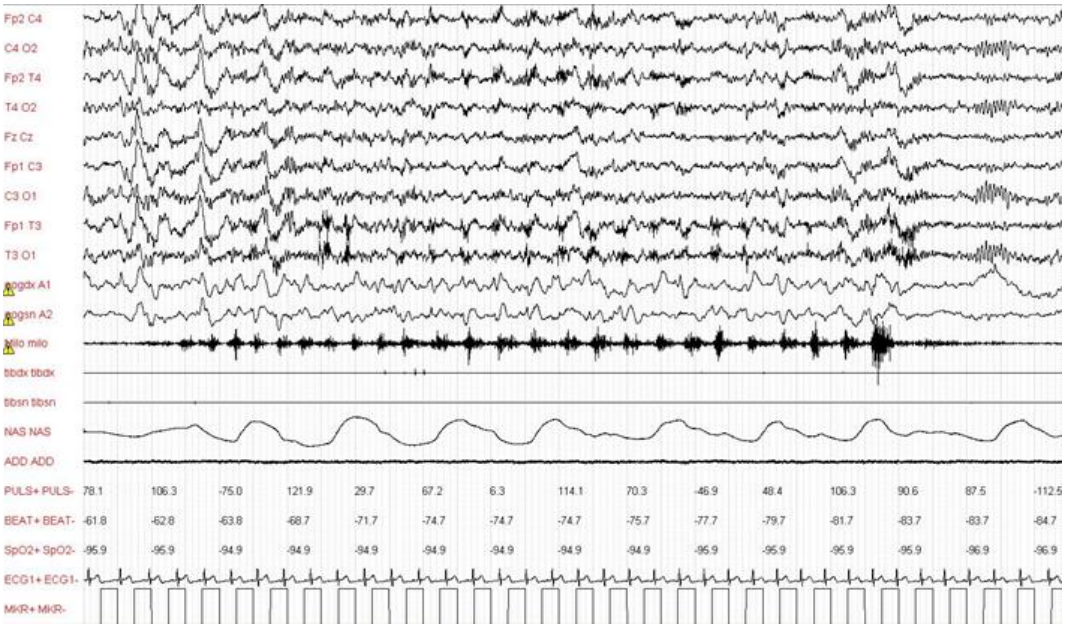

Figure 6: Epoch of N2 sleep showing sleep-related bruxism.
First 9 derivations, right and left electroencephalogram (EEG) derivations in a bipolar montage; eogdx, right electrooculogram; eogsn, left electrooculogram; milo, chin EMG channel; tibdx, right anterior tibialis; tibsn, left anterior tibialis; nas, oronasal airflow; torax, add, abdominal movements; ECG, electrocardiographic derivations; PULS pulse oximetry signal; BEAT, heart frequency; SpO2, oxygen saturation.

ALMA was defined as at least 4 brief activations of the anterior tibialis in one leg alternated with similar activation contralaterally, with a movement duration of 0.1–0.5 s and a frequency of 0.5–3 Hz, with sequences lasting between several and 20 s [65,67]. Other high frequency leg movements (HFLM) were not taken into account in our study [68] (Figure 7).

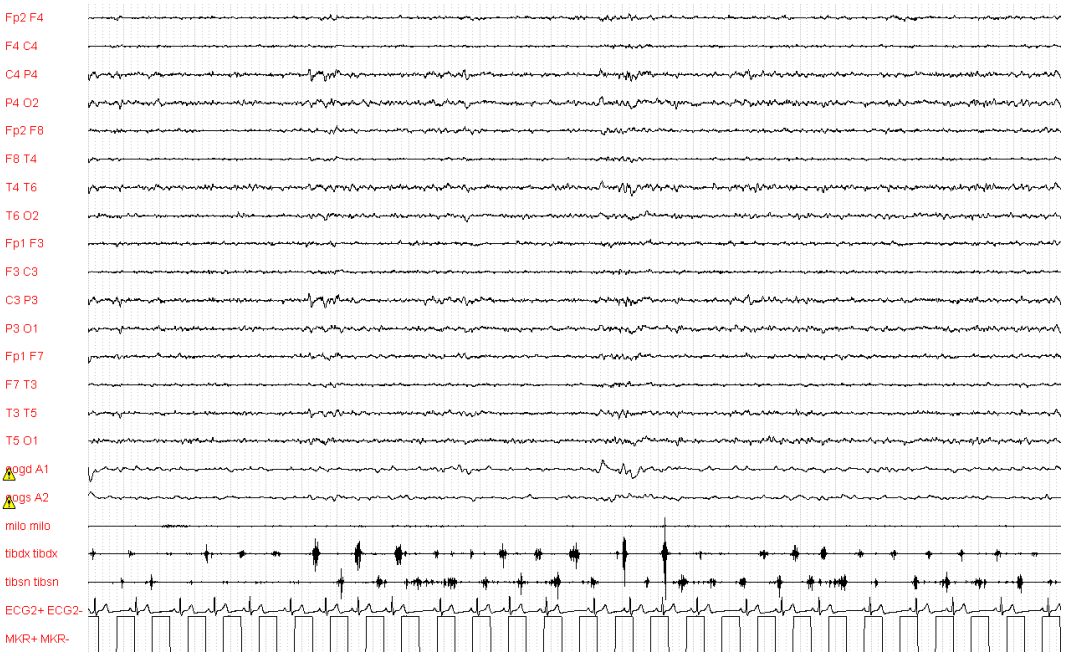

Figure 7: Epoch of N2 sleep showing alternating limb muscles activations (ALMA).
First 16 derivations, right and left electroencephalogram (EEG) derivations in a bipolar montage; eogdx, right electrooculogram; eogsn, left electrooculogram; milo, chin EMG channel; tibdx, right anterior tibialis; tibsn, left anterior tibialis; ECG, electrocardiographic derivations.

Neck myoclonus was considered as a “short stripe-shaped movement-induced artifact” visible vertically over the polysomnographic traces with a duration up to 2 s [56] (Figure 8).

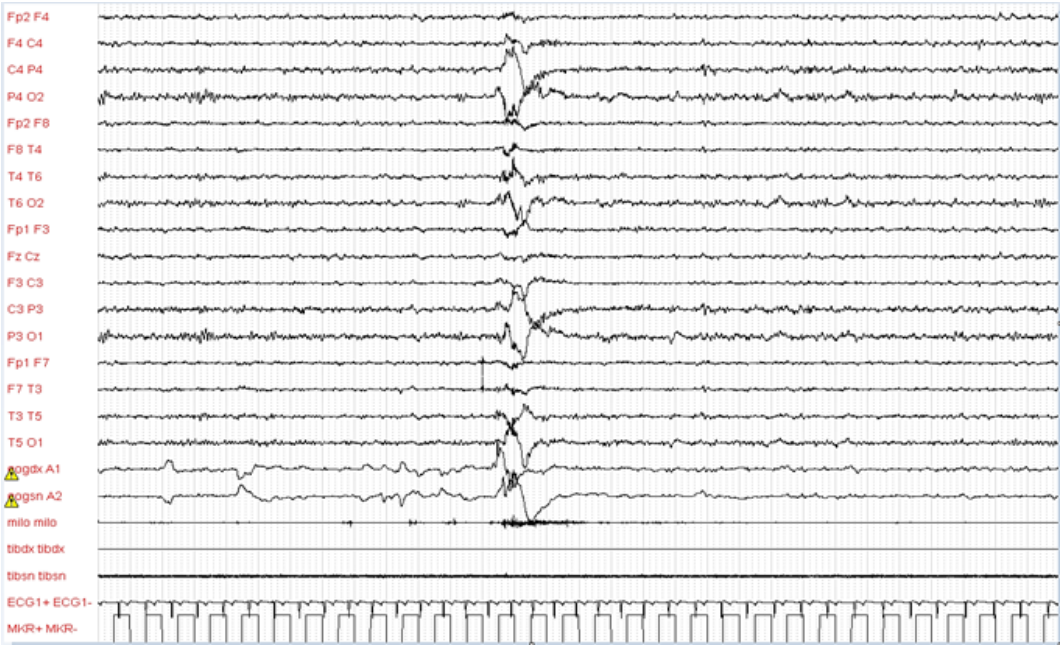

Figure 8: Epoch of REM sleep showing Neck myoclonus.
First 16 derivations, right and left electroencephalogram (EEG) derivations in a bipolar montage; eogdx, right electrooculogram; eogsn, left electrooculogram; milo, chin EMG channel; tibdx, right anterior tibialis; tibsn, left anterior tibialis; ECG, electrocardiographic derivations.

EFM was scored if at least 20 minutes of NREM sleep with EMG bursts on both legs of about 150 msec duration was recorded [65] (Figure 9).

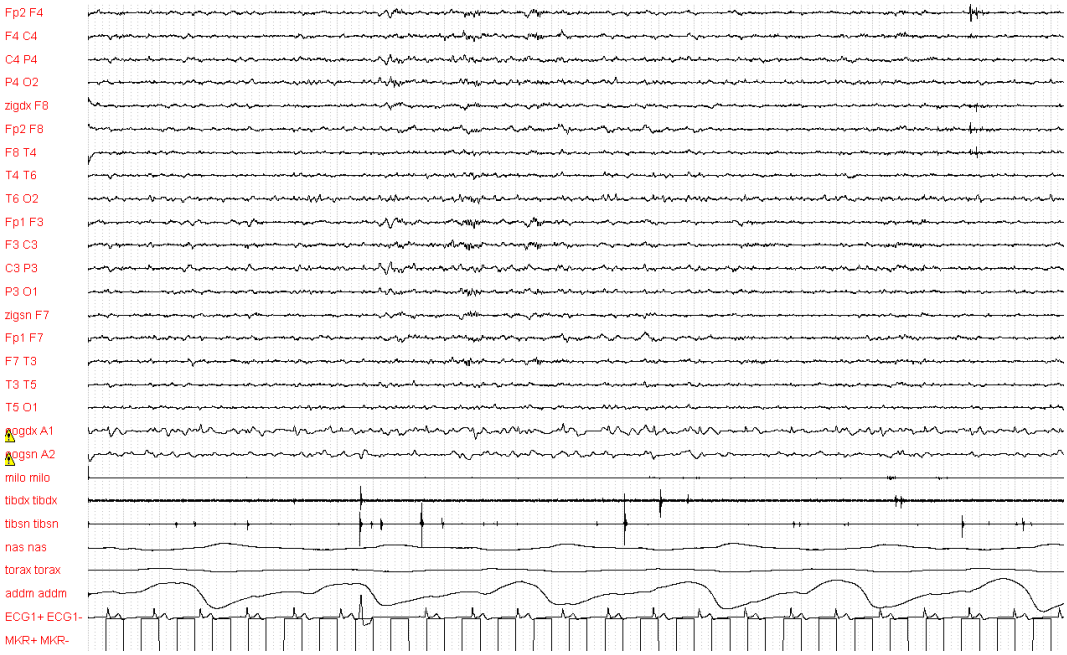

Figure 9: Epoch of NREM sleep showing excessive fragmentary myoclonus (EFM).
First 18 derivations, right and left electroencephalogram (EEG) derivations in a bipolar montage; eogdx, right electrooculogram; eogsn, left electrooculogram; milo, chin EMG channel; tibdx, right anterior tibialis; tibsn, left anterior tibialis; nas, oronasal airflow; torax, thoracic movements; add, abdominal movements; ECG, electrocardiographic derivations.

The nocturnal recordings comprised night-time sleep and awakening, as recommended for the SRE by the recently published standard procedures for the diagnostic pathway of sleep-related epilepsies and comorbid sleep disorders [7]. Moreover, in patients with IGE the presence of generalized EEG abnormalities was assessed and their presence during NREM (mainly N2 and N3) and REM sleep or at awakening was evaluated in the patients' group.

2.5 Ethics

All subjects signed a written informed consent. The study was approved by the local Ethical Committee (59/2020/PO). It was developed in accordance with the STROBE [69] guidelines for observational studies.

2.6 Statistics

Statistical analysis was performed using STATA 16 software packages (version 16.0, College Station, TX). Qualitative variables were described as percentages while quantitative variables as mean ± standard deviation (SD). Prior to statistical testing, the data were examined for normality using Shapiro-Wilk test. Pearson chi squared test (χ^2) or Fisher's exact test were employed to study categorical variables; comparison between means were performed using unpaired t test for parametric data and Mann-Whitney test for non-parametric data. Multiple comparison were corrected using Bonferroni method. A multivariate logistic regression was applied to identify predictive factors for all and each one of the sleep disorders in patients and controls, using variables with $P < 0.25$ in univariate calculations and retaining gender and age. The model was manually constructed using the likelihood ratio test (LRT) to compare the log-likelihood of the model with and without a specific variable. To evaluate the association with continuous

variables a linear regression model was applied. A $p < 0.05$ was set as level of significance.

2.7 Sample size calculation

Sample size calculation was based on the reported prevalence of the most common and studied among sleep disorders, PLM, which is 28.6% in the general population [70], with an estimated OR of 4.20 between patients with epilepsy and healthy controls, based on previous reports [71]. Thus, aiming for at least 80% power and an alpha level of 0.05, with a controls-cases ratio of 2:0, the minimum sample size required to find a difference has been calculated to be 25 cases and 49 controls (https://www.openepi.com/SampleSize/SSCC.htm).

3. Results

3.1 Patients with focal epilepsy vs controls

3.1.1 Clinical features of patients with focal epilepsy and controls

A total of 100 patients were studied (Table 1). Among patients with structural epilepsy, 12 (35.3%) had malformations of cortical development and neuronal migration defects such as periventricular nodular heterotopia, polymicrogyria, and focal cortical dysplasia, whereas six patients (17.6%) had hippocampal

sclerosis. Twelve subjects (30%) among patients with frontal lobe epilepsy had a diagnosis of sleep related hypermotor epilepsy (SHE). 33% of patients was drug resistant. 55% of patients had a clinical report of seizures during sleep. Regarding comorbidities, seven patients had dysthyroidism, five hypertension and two diabetes. Among subjects who were taking ASMs, 33 (50.8%) were on monotherapy, while of the remaining 32 (49.2%) on polytherapy, six (18.7%) were taking more than two ASMs.

Sixty-two subjects were studied as control group (Table 1). Comorbidities were hypertension for eight (12.9%), dysthyroidism for eight (12.9%), diabetes for three (4.8%) and one patient (1.6%) had chronic renal failure. Control subjects were slightly but significantly older than examined patients, whereas no differences were present in sex distribution or psychotropic drugs intake (Table 1).

Table 1: Demographic and clinical features of patients with focal epilepsy and controls

	Patients n=100	**Controls n=62**	**p**
Age (mean ± SD)	30.3 ± 14.7	36.4 ± 15.9	**0.01**
Sex (men) (%)	40 (40)	20 (32.2)	0.40
Age at seizure onset (mean ± SD)	20.2 ± 14.1	/	
Epilepsy type		/	
· Structural (%)	34 (34)		
· Unknown etiology (%)	64 (64)		
· Undetermined (%)	2 (2)		
Lobe of origin		/	
· Frontal (%)	40 (40)		
· Temporal (%)	53 (53)		
· Occipital (%)	5 (5)		
· Parietal (%)	2 (2)		
History of focal to bilateral tonic-clonic seizures	62 (62)	/	
Treatment during the recording			
· ASMs (%)	65 (65)	/	/
· Antidepressants (%)	6 (6)	9 (14.5)	0.07
· Benzodiazepines (%)	15 (15)	11 (17.4)	0.64
ASMs taken by the patients			
Carbamazepine (%)	19 (27.8)		
Clobazam (%)	5 (7)		
Felbamate (%)	1 (1.4)		
Lacosamide (%)	3 (4.2)		
Levetiracetam (%)	21 (29.5)		
Lamotrigine (%)	5 (7)		
Phenytoin (%)	3 (4.2)		
Phenobarbital (%)	9 (12.7)		
Primidone (%)	1 (1.4)		
Oxcarbazepine (%)	14 (19.7)		
Topiramate (%)	18 (25.3)		
Valproate (%)	11 (15.5)		
Zonisamide (%)	1 (1.4)		

Values in bold are those statistically significant.
N, number; SD, standard deviation; ASMs, antiseizure medications.

3.1.2 Sleep features of patients and controls

92% of patients and none of the controls presented EEG abnormalities during sleep. The sleep macrostructural parameters of patients and controls are described in Table 2. In particular, patients had significant lower total sleep time, longer sleep latency and lower REM sleep stage percentage than controls. At the multivariate analysis, adjusting for age and sex, higher TST was negatively associated with having epilepsy (Coeff=-55.2; 95%CI=-83.9- -26.5; p<0.01) as well as SE (Coeff=-5.3; 95%CI=-10.3- -0.4; p=0.03); higher SL was associated with having epilepsy (Coeff=6; 95%CI=0.9-11; p=0.02); REM sleep percentage was negatively associated with epilepsy (Coeff=-5.6; 95%CI=-7.6- -3.6; p=<0.001).

Table 2: Sleep macrostructural parameters in patients and controls

Sleep parameters	**Patients n=100**	**Controls n=62**	**p**
Total sleep time (minutes)	340.9 ± 87	395.9 ± 78.3	**<0.001**
Sleep efficiency (%)	84 ± 16.2	86.5 ± 9.6	0.78
Sleep latency (minutes)	19.2 ± 16	12.5 ± 12.9	**<0.001**
Wake after sleep onset (minutes)	52.5 ± 49.2	58.8 ± 43.7	0.17
N1%	5.5 ± 7.1	5.2 ± 5.9	0.02
N2%	51.1 ± 10.4	49.8 ± 5.6	0.19
N3%	27.8 ± 11.5	24.7 ± 6.2	0.16
REM%	15.2 ± 6.1	20.8 ±5.6	**<0.001**

Values in bold are those significant after Bonferroni correction (statistically significant: p≤0.006).

Seventy-three patients (73%) had a sleep disorder while 31% showed more than one sleep disorder (Table 2): in particular, in 24% of patients two sleep disorders were recorded and in 7% of patients three sleep disorders were recorded. The most frequent sleep disorders recorded were sleep-related movement disorders (40%) while normal sleep variants were present in 41% of patients (Table 3).

Among 62 controls, 40 (64.5%) underwent a complete VPSG while for the remaining 22 (35.5%) video was not available. In 30 (48.4%) of controls a sleep disorder was recorded while 7 (11.3%) showed more than one sleep disorder: in particular, in 4 (6.4%) of patients two sleep disorders were recorded and in 3 (4.8%) three sleep disorders were present. The most frequent sleep disorder recorded was DoA in 17 subjects (27.4%) while normal sleep variants were present in 14 subjects (22.6%) and sleep-related movement disorders in 5 (8.1%) (Table 3). Comparing the percentages of sleep disorders between patients and controls, we found a significant higher percentage of sleep disorders in patients (73% vs 48.4%; p=0.002). More specifically we found a higher frequency of PLM, bruxism and neck myoclonus in patients compared to controls, as shown in Table 3 and Figure 10.

Table 3 - Sleep disorders recorded in patients and controls**.**

Sleep disorders	**Patients n=100**	**Controls n=62**	**p**
Disorders of arousal, n (%)	26 (26)	17 (27.4)	0.84
Rem Behavior Disorder, n (%)	1 (1)*	0	0.43
Periodic Limb Movements, n (%)†	20 (20)	3 (4.8)	**0.007**
Bruxism, n (%)	20 (20)	3 (4.8)	**0.007**
Alternating leg muscle activation, n (%)	17 (17)	9 (14.5)	0.67
Excessive fragmentary myoclonus, n (%)	4 (4)	4 (6.4)	0.48
Neck myoclonus, n (%)	22 (22)	3 (4.8)	**0.003**

Values in bold are those significant after Bonferroni correction (statistically significant: $p \leq 0.007$).

* The patient with RBD presented also REM sleep without atonia (RSWA).

† Mean PLM index of 36.5 ± 21.5 in patients and 23.9 ± 4.8 in controls.

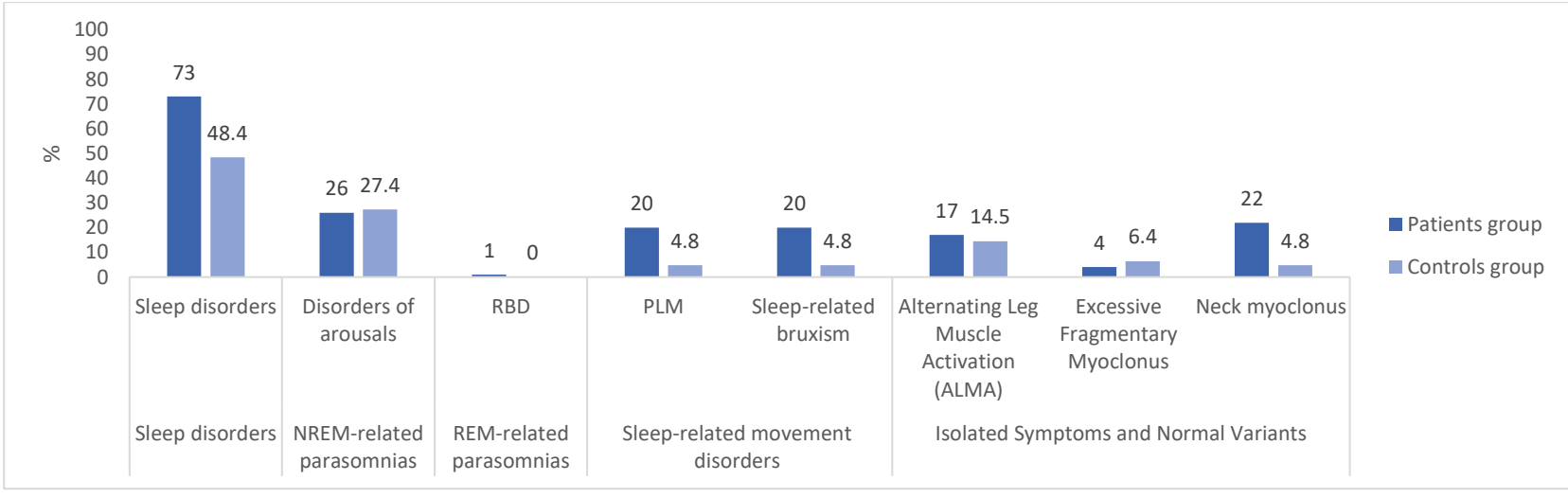

Figure 10: Percentages of sleep disorders in patients with focal epilepsy and controls.

At the multivariate analysis, after adjusting for age, sex and use of benzodiazepines and antidepressants, the associations between epilepsy and sleep disorders, PLM, bruxism and neck myoclonus were confirmed (Table 4).

Table 4: Univariate and multivariate analysis of sleep disorders in patients and controls.

	SD+	SD-	Univariate analysis			Multivariate analysis		
	N= 103	**N= 59**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	30.2±15.8	36.7±13.9	0.97	0.95-0.99	**0.008**	0.98	0.95-1	0.09
Sex (men) (%)	47 (45.6)	13 (22.03)	3	1.4-6.1	**0.003**	2.5	1.1-5.4	**0.02**
Epilepsy (%)	73 (70.8)	27 (45.8)	2.9	1.5-5.6	**0.002**	2.6	1.3-5.2	**0.008**
Benzodiazepines (%)	11 (10.7)	15 (25.4)	0.3	0.1-0.8	**0.02**	0.4	0.2-1.1	0.09
Antidepressants (%)	7 (6.8)	8 (13.6)	0.5	0.1-1.3	0.16			
	DoA+	**DoA-**	**Univariate analysis**			**Multivariate analysis**		
	N= 43	**N= 119**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	22.3±6.6	36.4±15.9	0.9	0.8-0.9	**<0.001**	0.9	0.8-0.9	**<0.001**
Sex (men) (%)	16 (37.2)	44 (37)	1	0.5-2.1	0.97	0.6	0.2-1.4	0.22
Epilepsy (%)	26 (60.5)	74 (62.2)	0.9	0.4-1.9	0.84			
Benzodiazepines (%)	2 (4.6)	24 (20.2)	0.2	0.04-0.8	**0.03**	0.2	0.04-1.1	0.07
Antidepressants (%)	1 (2.3)	14 (11.8)	0.2	0.02-1.4	**0.10**	1.1	0.1-10.5	0.95
	PLM+	**PLM-**	**Univariate analysis**			**Multivariate analysis**		
	N= 23	**N= 139**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	41.9±14.3	31.1±15.1	1.04	1.01-1.07	**0.003**	1.05	1.02-1.08	**<0.001**
Sex (men) (%)	7 (30.4)	53 (38.1)	0.7	0.3-1.8	0.48	0.6	0.2-1.8	0.42
Epilepsy (%)	20 (87)	80 (57.5)	4.9	1.3-17.3	**0.01**	8.7	2.2-34.9	**0.002**
Benzodiazepines (%)	5 (21.7)	21 (15.1)	1.6	0.4-4.7	0.42			
Antidepressants (%)	4 (17.4)	11 (7.9)	2.4	0.7-8.5	0.16			
	Bruxism+	**Bruxism-**	**Univariate analysis**			**Multivariate analysis**		
	N= 23	**N= 139**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	23.6±9	34.2±15.8	0.93	0.89-0.98	**0.004**	0.94	0.90-0.99	**0.02**
Sex (men) (%)	14 (60.9)	46 (33.1)	3.1	1.3-7.8	**0.01**	2.7	1-7	**0.04**
Epilepsy (%)	20 (87)	80 (57.5)	4.9	1.4-17.3	**0.01**	3.9	1-14.2	**0.04**
Benzodiazepines (%)	4 (17.4)	22 (15.8)	1.1	0.3-3.6	0.85			
Antidepressants (%)	1 (4.3)	14 (10.1)	0.4	0.05-3.2	0.39			
	ALMA+	**ALMA-**	**Univariate analysis**			**Multivariate analysis**		
	N= 26	**N= 136**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	26.2±9.8	33.9±16	0.96	0.93-0.99	**0.03**	0.95	0.90-0.99	**0.02**
Sex (men) (%)	14 (53.8)	46 (33.8)	2.3	1-5.3	**0.06**	2.1	0.8-5.1	0.11
Epilepsy (%)	17 (65.4)	83 (61)	1.2	0.5-2.9	0.68			
Benzodiazepines (%)	2 (7.7)	24 (17.6)	0.4	0.1-1.7	0.22	0.3	0.05-1.7	0.18
Antidepressants (%)	4 (15.4)	11 (8.1)	2.1	0.6-7.1	0.25	8.4	1.7-41.9	**0.01**
	NM+	**NM-**	**Univariate analysis**			**Multivariate analysis**		
	N= 25	**N= 137**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	25.1±9.7	34±15.9	0.95	0.91-0.98	**0.01**	0.96	0.92-0.99	**0.04**
Sex (men) (%)	12 (48)	48 (35)	1.7	0.7-4	0.22	1.4	0.6-3.5	0.45
Epilepsy (%)	22 (88)	78 (56.9)	5.5	1.6-19.4	**0.007**	4.5	1.3-16.2	**0.02**
Benzodiazepines (%)	3 (12)	23 (16.8)	0.7	0.2-2.4	0.55			
Antidepressants (%)	1 (4)	14 (10.2)	0.4	0.04-2.9	0.34			
	EFM+	**EFM-**	**Univariate analysis**			**Multivariate analysis**		
	N= 8	**N= 154**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	56.1±14	31.4±13.9	1.08	1.04-1.13	**<0.001**	1.1	1.04-1.15	**<0.001**
Sex (men) (%)	6 (75)	54 (35.1)	5.5	1.2-28.5	**0.04**	10.8	1.6-73.3	**0.01**
Epilepsy (%)	4 (50)	96 (62.3)	0.6	0.1-2.5	0.48			
Benzodiazepines (%)	1 (12.5)	25 (16.2)	0.7	0.1-6.2	0.78			
Antidepressants (%)	0	15 (9.7)						

CI, confidence intervals; OR, odds ratio; SD, sleep disorders; DoA, disorders of arousal; PLM, periodic limb movements; ALMA, alternating leg muscle activation; NM, neck myoclonus; EFM, excessive fragmentary myoclonus.

3.1.3 Sleep features of patients

When performing the multivariate analysis in the group of patients in order to evaluate the influence of demographical features and specific epilepsy-related variables on sleep disorders, we found that the presence of a DoA was associated with a younger age (OR= 0.9; 95%CI=0.8-0.9; p=0.01) as well as bruxism (OR= 0.9; 95%CI= 0.9-0.99; p= 0.03). PLM was significantly associated with a higher age (OR=1.1; 95%CI=1-1.2; p=0.01) as well as EFM (OR=1.1; 95%CI=1.0-1.2; p= 0.02); moreover, PLM was associated with the use of antidepressants (OR=13.1; 95%CI=1-178.4; p=0.05). ALMA was associated with male sex (OR=3.5; 95%CI=1-11.8; p=0.04) and sleep-related hypermotor epilepsy (SHE) (OR= 7.9; 95%CI=1.8-34.6; p=0.01). In fact, ALMA was present in 50% of SHE patients (Tables 5-9). The presence of EEG abnormalities during sleep was not associated with having a sleep disorder (OR=0.4; 95%CI=0.5-3.7; p=0.44).

3.1.4 Effect of ASMs on sleep disorders

In the subgroup of patients taking ASMs (65%) (mean age 32.2 ± 14.3 years, 26 men), we evaluated the association between ASMs and sleep disorders, after adjusting for age and sex.

Levetiracetam was found to be negatively associated with the presence of sleep disorders (OR=0.09; 95%CI=0.01-0.48; p=0.004), especially PLM (OR=0.04;

95%CI=0.002-0.5; p=0.01) while topiramate use was positively associated with it (OR=5.2; 95%CI=1-26.5; p=0.05).

Table 5: Multivariate analysis in patients according to the presence of recorded DoA.

	DoA+ n=26	**DoA- n=74**	**Univariate analysis**			**Multivariate analysis**		
			OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	21.3±6.8	33.5±15.5	0.9	0.8-0.9	**0.001**	0.9	0.8-0.9	**0.01**
Sex (men) (%)	11 (42.3)	29 (39.2)	1.1	0.4-2.8	0.78	0.8	0.3-2.2	0.39
Age at onset (mean ± SD)	16.1±8.5	21.7±15.3	0.9	0.9-1	0.08			
Focal to bilateral tonic-clonic seizures (%)	18 (69.2)	44 (59.5)	1.5	0.6-3.9	0.38			
Seizures in sleep (%)	16 (61.5)	39 (52.7)	1.4	0.6-3.6	0.44			
Epilepsy type (%)			2.7	1-66.8	**0.04**	2.1	0.7-6	0.17
Structural	13 (52)	21 (28.8)						
Unknown etiology	12 (48)	52 (71.2)						
Undetermined	0 (0)	2 (2.7)						
Lobe of origin (%)								
Temporal	10 (38.4)	43 (58.1)	0.4	0.2-1.1	0.09	0.6	0.2-1.8	0.39
Frontal	13 (50)	27 (36.5)	1.7	0.7-4.3	0.23			
Occipital	2 (7.7)	3 (4)	1.9	0.3-12.5	0.47			
Parietal	1 (3.8)	1 (1.3)	2.9	0.2-48.4	0.45			
SHE	3 (11.5)	9 (12.6)	0.9	0.2-3.8	0.93			
Treatment (%)								
ASM	16 (61.5)	49 (66.2)	0.8	0.3-2.1	0.67			
Benzodiazepines	2 (7.7)	13 (17.6)	0.4	0.8-1.8	0.23	0.7	0.1-3.9	0.67
Antidepressants	1 (3.8)	5 (6.8)	0.5	0.1-4.9	0.60			

N, number; CI, confidence intervals; OR, odds ratio; SHE, sleep related hypermotor seizures; ASMs, antiseizure medications; DoA, disorders of arousal.

Table 6: Multivariate analysis in patients according to the presence of recorded PLM.

	PLM+ n=20	**PLM- n=80**	**Univariate analysis**		**Multivariate analysis**			
			OR	**95%CI**	**p**	**OR**	**95%CI**	**p**
Age (mean ± SD)	43±14.2	27.2±13.1	1.1	1.0-1.1	**<0.001**	1.1	1-1.2	**0.01**
Sex (men) (%)	6 (15)	34 (85)	0.6	0.2-1.7	0.31	0.6	0.1-2.6	0.47
Age at onset (mean ± SD)	28.3±18.5	18.2±12	1	1.0-1.1	**0.008**	0.9	0.9-1	0.29
Focal to bilateral tonic-clonic seizures (%)	14 (22.6)	48 (77.4)	1.6	0.5-4.5	0.41			
Seizures in sleep (%)	6 (10.9)	49 (89.1)	0.3	0.1-0.8	**0.02**	0.24	0-0.9	**0.05**
Epilepsy type (%)			0.5	0.1-1.6	0.22			
Structural	4 (11.8)	30 (88.2)						
Unknown	14 (21.9)	59 (78.1)						
Undetermined	2 (100)	0 (0)						
Lobe of origin (%)								
Temporal	13 (24.5)	40 (75.5)	1.9	0.7-5.1	0.23			
Frontal	6 (15)	34 (85)	0.6	0.2-1.7	0.31			
Occipital	1 (20)	4(80)	1	0.1-9.5	1			
Parietal	0 (0)	2 (100)	/	/	/			
SHE	0 (0)	12 (100)	/	/	/			
Treatment (%)								
ASMs	15 (23.1)	50 (76.9)	1.8	0.6-5.4	0.29			
Benzodiazepines	5 (33.3)	10 (66.7)	2.5	0.7-8.4	0.14	6.6	0.8-51.7	0.07
Antidepressants	3 (50)	3 (50)	4.5	0.8-24.4	0.08	13.1	1-178.4	**0.05**

N, number; CI, confidence intervals; OR, odds ratio; SHE, sleep related hypermotor seizures; ASMs, antiseizure medications; PLM, periodic limb movements.

Table 7: Multivariate analysis in patients according to the presence of recorded sleep-related bruxism.

	Bruxism+ n=20	**Bruxism- n=80**	**Univariate analysis**			**Multivariate analysis**		
			OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	22.7±8.6	32.2±15.3	0.9	0.9-1	**0.01**	0.9	0.9-0.99	**0.03**
Sex (men) (%)	12 (30)	28 (70)	2.8	1-7.6	**0.05**	2.6	0.9-7.4	0.08
Age at onset (mean ± SD)	15.1±6.9	21.5±15.1	0.9	0.9-1	0.07			
Focal to bilateral tonic-clonic seizures (%)	14 (22.6)	48 (77.4)	1.5	0.5-4.5	0.41			
Seizures in sleep (%)	13 (23.6)	42 (76.4)	1.7	0.6-4.6	0.32			
Epilepsy type (%)			2.2	0.8-6.1	0.11			
Structural	10 (29.4)	24 (70.6)						
Unknown	10 (15.6)	54 (84.4)						
Undetermined	0 (0)	2 (100)						
Lobe of origin (%)								
Temporal	10 (18.9)	43 (81.1)	0.9	0.3-2.3	0.76			
Frontal	8 (20)	32 (80)	1	0.4-2.7	1			
Occipital	2 (40)	3 (60)	2.8	0.4-18.3	0.27			
Parietal	0 (9)	2 (100)	/	/	/			
SHE	2 (16.7)	10 (83.3)	0.8	0.1-3.9	0.76			
Treatment (%)								
ASMs	14 (21.5)	51 (78.5)	1.3	0.5-3.8	0.60			
Benzodiazepines	4 (26.7)	11 (73.3)	1.5	0.4-5.5	0.50			
Antidepressants	1 (16.7)	5 (83.3)	0.8	0.1-7.1	0.83			

N, number; CI, confidence intervals; OR, odds ratio; SHE, sleep related hypermotor seizures; ASMs, antiseizure medications.

Table 8: Characteristics of the patients according to the presence of ALMA.

	ALMA+ n=17	**ALMA- n=83**	**Univariate analysis**			**Multivariate analysis**		
			OR	**95%CI**	**p**	**OR**	**95%CI**	**P**
Age (mean ± SD)	23.1±8.3	31.8±15.3	0.9	0.8-0.9	**0.03**	0.9	0.9-1.0	0.25
Sex (men) (%)	11 (64.7)	29 (34.9)	3.4	1.1-10.2	**0.03**	3.5	1.0-11.8	**0.04**
Age at onset (mean ± SD)	15.2±8.7	21.2±14.7	0.9	0.9-1.0	0.1			
Focal to bilateral tonic-clonic seizures (%)	12 (70.5)	50 (60.2)	1.6	0.5-4.9	0.4			
Seizures in sleep (%)	13 (76.5)	42 (50.6)	3.2	0.9-10.5	0.06			
Epilepsy type (%)			0.5	0.1-1.75	0.29			
Structural	4 (23.5)	30 (37)						
Unknown	13 (76.5)	51 (63)						
Undetermined	0 (0)	2 (2.4)						
Lobe of origin (%)								
Temporal	7 (41.2)	46 (55.4)	0.6	0.2-1.6	0.29			
Frontal	10 (58.8)	30 (36.1)	2.5	0.9-7.3	0.09			
Occipital	0 (0)	5 (6)	/	/	/			
Parietal	0 (0)	2 (2.4)	/	/	/			
SHE	6 (35.3)	6 (7.2)	7	1.9-25.6	**0.003**	7.86	1.8-34.6	**0.01**
Treatment (%)								
ASMs	12 (70.6)	53 (63.9)	1.4	0.4-4.2	0.60			
Benzodiazepines	1 (5.9)	14 (16.9)	0.3	0.0-2.5	0.27			
Antidepressants	1 (5.9)	5 (6)	0.9	0.1-8.9	0.98			

N, number; CI, confidence intervals; OR, odds ratio; SHE, sleep related hypermotor seizures; ASMs, antiseizure medications; ALMA, alternating limb muscle activation**.**

Table 9: Characteristics of the patients according to the presence of NM.

	NM+ n=22	NM- n=78	Univariate analysis			Multivariate analysis		
			OR	95%CI	p	OR	95%CI	p
Age (mean ± SD)	24.4±9.9	32.0±15.5	0.9	0.9-0.99	**0.04**	0.9	0.9-1	0.28
Sex (men) (%)	10 (45.4)	30 (38.5)	1.3	0.5-3.5	0.55	1.3	0.5-3.6	0.61
Age at onset (mean ± SD)	15±8.4	21.7±15	0.95	0.9-1	0.05			
Focal to bilateral tonic-clonic seizures (%)	12 (54.5)	50 (64.1)	0.67	0.2-1.7	0.41			
Seizures in sleep (%)	14 (63.6)	41 (52.6)	1.6	0.6-4.2	0.36			
Epilepsy type (%)			1.4	0.5-3.7	0.5			
Structural	9 (40.9)	25 (32.9)						
Unknown	13 (59.1)	51 (67.1)						
Undetermined	0 (0)	2 (2.6)						
Lobe of origin (%)								
Temporal	7 (31.8)	46 (59)	0.32	0.1-0.9	0.03	0.4	0.1-1	0.06
Frontal	11 (50)	29 (37.2)	1.7	0.6-4.4	0.3			
Occipital	2 (9.1)	3 (3.8)	2.5	0.4-16	0.3			
Parietal	2 (9.1)	0 (0)	/	/	/			
SHE	4 (18.2)	8 (10.3)	1.9	0.5-7.2	0.3			
Treatment (%)								
ASMs	12 (54.5)	53 (67.9)	0.6	0.2-1.5	0.25	0.7	0.3-2.1	0.57
Benzodiazepines	3 (13.6)	12 (15.4)	0.8	0.2-3.3	0.8			
Antidepressants	1 (4.5)	5 (6.4)	0.7	0.1-6.3	0.74			

N, number; CI, confidence intervals; OR, odds ratio; SHE, sleep related hypermotor seizures; ASMs, antiseizure medications; NM, neck myoclonus.

3.2 Patients with IGE vs controls

3.2.1 Clinical features of patients with IGE and controls

Thirty-five patients with IGE were studied. Their clinical features are described in Table 10. A cognitive assessment was available for 20 out of 35 patients (57.1%). An MRI was available for all except two patients (5.7%) and it showed abnormalities only in eight (24.2%). In particular, two had a mild cortical atrophy, two had aspecific gliotic alterations, one patient had an arachnoid cyst, one had an empty sella, one had an Arnold Chiari Syndrome type I, one a third ventricle colloid cyst. As shown in Table 10, 22 (62.9%) were taking ASMs with a median of 1 drug used during the recording (range 0-3). For all except five patients a follow-up with at least two years-observation was available with a mean follow-up time of 9.6 ± 6.9 years, and among these patients, 10 (33.3%) were drug resistant. Eight (22.8%) patients reported comorbidities, two had dysthyroidism, one hypertension, one obesity, one venous insufficiency in the lower limbs, one migraine and two other endocrinopathies.

Fifty-six controls were studied. Comorbidities were present in eleven (19.6%) and were: hypertension for four, dysthyroidism for three, nephropathy for two and diabetes and migraine for one (4.8%). Only one of them (1.8%) was using an ASM for migraine prophylaxis. Their features are shown in Table 10.

Table 10: Demographic and clinical features of patients with IGE and controls.

Variables N (%)	**Patients n=35**	**Controls n=56**	**p**
Age (mean ± SD)	28.8 ± 13.1	32.8 ± 11.5	0.13
Sex (men) (%)	11 (31.4)	18 (32.1)	0.94
Age at seizure onset (years) (mean ±	14.3 ± 6.1	/	
Family history of epilepsy (%)	14 (40)	/	
Mild intellectual deficit (%)	3/20 (15)	/	
Abnormal MRI (%)	8/33 (24.2)	/	
Status epilepticus in the history (%)	3 (8.6)	/	
Epilepsy type		/	
· Juvenile Myoclonic Epilepsy (%)	19 (54.3)		
· Juvenile Absence epilepsy (%)	4 (11.4)		
· Generalized Tonic-Clonic Seizures	8 (22.9)		
· Eyelid Myoclonia with absences (%)	4 (11.4)		
Seizure types		/	
· GTCS (%)	29 (82.9)		
· Absences (%)	19 (54.3)		
· Eyelid myoclonia (%)	5 (14.3)		
· Limbs myoclonia (%)	17 (48.6)		
Photosensitivity (%)	34 (97.1)	/	
Eye closure sensitivity (%)	7 (20)	/	
Treatment during the recording			
· ASMs (%)	22 (62.9)	1 (1.8)	**<0.001**
· Antidepressants (%)	4 (11.4)	7 (12.5)	0.58
· Benzodiazepines (%)	4 (11.4)	10 (17.8)	0.55
Drug resistance (%)	10 (33.3)	/	
Seizure freedom at the last follow-up	14 (46.7)	/	
ASMs taken by the patients			
Carbamazepine (%)	1 (2.9)		
Clobazam (%)	3 (8.6)		
Clonazepam (%)	1 (2.9)		
Ethosuximide (%)	1 (2.9)		
Levetiracetam (%)	9 (40.9)		
Lacosamide (%)	1 (2.9)		
Lamotrigine (%)	8 (36.4)		
Oxcarbazepine (%)	2 (5.7)		
Phenobarbital (%)	4 (11.4)		
Topiramate (%)	2 (5.7)	1 (1.8)	/
Valproate (%)	9 (40.9)		
Zonisamide (%)	1 (2.9)		

N, number; SD, standard deviation; MRI, magnetic resonance imaging; GTCS, generalized tonic-clonic seizures; ASMs, antiseizure medications.

3.2.2 Sleep features of patients and controls

Twenty-eight patients (80%) presented EEG abnormalities during sleep, 26 of them (92.8%) during NREM sleep, four (14.2%) during REM sleep, 11 (39.2%) at awakening.

The comparison between macrostructural parameters of patients and controls demonstrated a significant lower TST, higher sleep latency and N2 sleep, lower N1 and REM sleep percentage in the group of patients (Table 11). These differences were confirmed after adjusting for sex and age, except for lower N1 sleep percentage (p=0.12).

Table 11: Sleep macrostructural parameters in patients and controls

Sleep parameters	**Patients n=35**	**Controls n=56**	**p**
Total sleep time (minutes)	367.5 ± 86.9	398.9 ± 76.8	**0.05**
Sleep efficiency (%)	84.3 ± 11.5	87.8 ± 8.2	0.55
Sleep latency (minutes)	27.3 ± 23.4	12.6 ± 12.9	**<0.01**
Wake after sleep onset	66 ± 57.1	52.6 ± 36	0.76
N1%	3.3 ± 3.1	5.3 ± 6.2	**0.01***
N2%	54.1 ± 8.3	49.7 ± 5.8	**0.01***
N3%	25 ± 8.1	24.4 ± 6.1	0.63
REM%	16.8 ± 6.6	21.1 ±5.2	**<0.01***

* Statistically significant after Bonferroni correction (statistically significant: p≤0.01)

In 29 (82.9%) patients a sleep disorder was recorded while 16 (45.7%) showed two sleep disorders and four (11.4%) three sleep disorders. The most frequent sleep disorders recorded in patients were: DoA in 21 (60%) of patients, normal sleep variants in 13 (37.1%), while sleep-related movements disorders were present in 11 (31.4%) (Table 12). Among 56 controls, in 28 (50%) a sleep disorder was recorded while 7 (12.5%) showed more than one sleep disorder and three (5.4%) three sleep disorders. The most frequent sleep disorders recorded were: DoA in 17 subjects (30.3%) while normal sleep variants were present in 12 subjects (21.4%) and sleep-related movement disorders in 5 (8.9%) (Table 12). None among patients and controls presented RBD.

Comparing the percentages of sleep disorders between patients and controls, a significant higher percentage of sleep disorders was found in patients (82.9% vs 50%, $p<0.01$) compared to controls. In particular, we found a higher frequency of DoA, bruxism and neck myoclonus in patients with IGE, as compared to controls (Table 12) (Figure 11).

Table 12: Sleep disorders recorded in patients and controls.

Sleep parameters	**Patients n=35**	**Controls n=56**	**p**
Disorders of arousal, n (%)	21 (60)	17 (30.3)	**0.008**
Rem Behavior Disorder (%)	0	0	/
Periodic Limb Movements, n (%)*	4 (11.4)	3 (5.4)	0.42
Bruxism, n (%)	10 (28.6)	3 (5.4)	**0.004**
Alternating leg muscle activation, n (%)	5 (14.3)	9 (16.1)	0.82
Excessive fragmentary myoclonus, n (%)	0	2 (3.6)	1
Neck myoclonus, n (%)	9 (25.7)	3 (5.4)	**0.009**

Values in bold are those statistically significant.

*Mean PLM index of 22.4 ± 3.4 in patients and 23.9 ± 5.8 in controls.

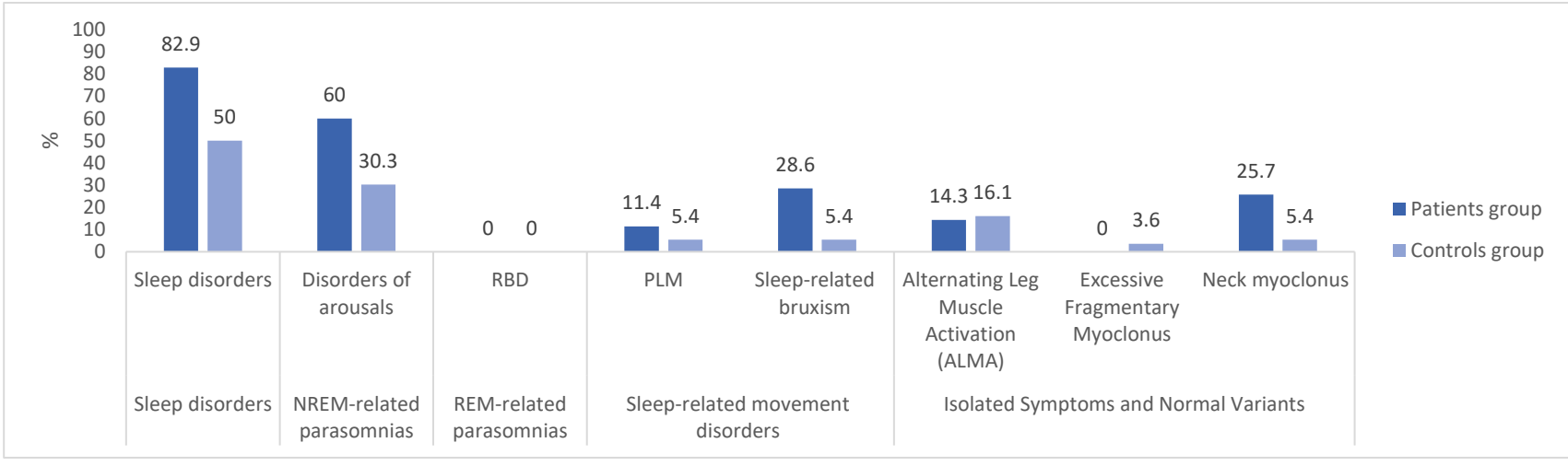

Figure 11: Percentages of sleep disorders in patients with IGE and controls.

At the multivariate analysis, after adjusting for age, sex and use of benzodiazepines and antidepressants, to identify predictive factors for all and each one of the sleep disorders in patients and control, the associations between epilepsy and sleep disorders, DoA, bruxism and neck myoclonus have been confirmed (Table 13).

Table 13: Univariate and multivariate analysis of sleep disorders in patients and controls.

	SD+	SD-	Univariate analysis			Multivariate analysis		
	N= 57	**N= 34**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	27.6±11.5	37.3±11.1	0.93	0.9-0.96	**<0.01**	0.93	0.88-0.97	**0.001**
Sex (men) (%)	19 (33.3)	10 (29.4)	0.83	0.3-2.1	0.70	1.2	0.4-3.5	0.73
Epilepsy (%)	29 (50.9)	6 (17.6)	4.8	1.7-13.4	**0.003**	4.9	1.5-15.7	**0.008**
Benzodiazepines (%)	4 (7.0)	10 (29.4)	0.2	0.05-0.6	**0.008**	0.1	0.02-0.7	**0.017**
Antidepressants (%)	5 (8.8)	6 (17.6)	0.4	0.1-1.6	0.22			
	DoA+	**DoA-**	**Univariate analysis**			**Multivariate analysis**		
	N= 38	**N= 53**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	24.0±9.8	36.4±11.2	0.9	0.8-0.9	**<0.001**	0.9	0.8-0.9	**<0.001**
Sex (men) (%)	13 (34.2)	16 (30.2)	0.8	0.3-2.0	0.68	1.3	0.4-4.0	0.65
Epilepsy (%)	21 (55.3)	14 (26.4)	3.4	1.4-8.3	**0.006**	3.7	1.2-11.6	**0.02**
Benzodiazepines (%)	1 (2.6)	13 (24.5)	0.8	0.1-0.7	**0.02**	0.07	0.006-0.8	**0.03**
Antidepressants (%)	1 (2.6)	10 (18.9)	0.1	0.01-0.9	**0.04**	0.5	0.03-5.6	0.54
	PLM+	**PLM-**	**Univariate analysis**			**Multivariate analysis**		
	N= 7	**N= 84**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	36.4±18.1	30.8±11.6	1.03	0.9-1.1	0.25	1.05	0.9-1.1	0.14
Sex (men) (%)	4 (57.1)	25 (29.8)	0.3	0.06-1.5	0.15	0.2	0.04-1.2	0.09
Epilepsy (%)	4 (57.1)	31 (36.9)	2.3	0.5-10.9	0.30			
Benzodiazepines (%)	0 (0)	14 (16.7)	/	/	/			
Antidepressants (%)	1 (14.3)	10 (11.9)	1.2	0.1-11.3	0.85			
	Bruxism+	**Bruxism-**	**Univariate analysis**			**Multivariate analysis**		
	N= 13	**N= 78**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	27.7±11.1	31.8±12.3	0.97	0.9-1.0	0.26	0.98	0.93-1.04	0.54
Sex (men) (%)	5 (38.5)	24 (30.8)	0.7	0.2-2.4	0.58	0.7	0.2-2.6	0.59
Epilepsy (%)	10 (76.9)	25 (32.0)	7.1	1.8-27.9	**0.005**	6.8	1.7-27.2	**0.007**
Benzodiazepines (%)	1 (7.7)	13 (16.7)	0.4	0.5-3.5	0.41			
Antidepressants (%)	1 (7.7)	10 (12.8)	0.6	0.06-4.8	0.60			
	ALMA+	**ALMA-**	**Univariate analysis**			**Multivariate analysis**		
	N=14	**N= 77**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	31.4±9.9	31.2±12.6	1.0	0.9-1.0	0.95	1.0	0.9-1-0	0.99
Sex (men) (%)	4 (28.6)	52 (67.5)	1.2	0.3-4.2	0.77	1.2	0.3-4.3	0.78
Epilepsy (%)	5 (35.7)	30 (38.9)	1.2	0.3-2.8	0.82			
Benzodiazepines (%)	1 (7.1)	13 (16.9)	0.4	0.04-3.1	0.37	0.3		
Antidepressants (%)	2 (14.3)	9 (11.7)	1.2	0.2-6.5	0.78	8.4		
	NM+	**NM-**	**Univariate analysis**			**Multivariate analysis**		
	N= 12	**N= 79**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	25.5±7.6	32.1±12.6	0.95	0.89-1.0	**0.09**	0.96	0.90-1.0	0.20
Sex (men) (%)	4 (33.3)	25 (31.6)	0.9	0.2-3.4	0.91	1.0	0.2-4.0	0.98
Epilepsy (%)	9 (75)	26 (32.9)	6.1	1.5-24.5	**0.01**	5.3	1.3-21.9	**0.02**
Benzodiazepines (%)	2 (16.7)	12 (15.2)	1.1	0.2-5.7	0.89			
Antidepressants (%)	1 (8.3)	10 (12.7	0.6	0.07-5.4	0.67			
	EFM+	**EFM-**	**Univariate analysis**			**Multivariate analysis**		
	N= 2	**N= 89**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	27±18.4	31.3±12.2						
Sex (men) (%)	2 (100)	27 (30.3)						
Epilepsy (%)	0	35 (39.3)						
Benzodiazepines (%)	0	14 (15.7)						
Antidepressants (%)	0	12 (13.5)						

CI, confidence intervals; OR, odds ratio; SD, sleep disorders; DoA, disorders of arousal; PLM, periodic limb movements; ALMA, alternating leg muscle activation; NM, neck myoclonus; EFM, excessive fragmentary myoclonus.

3.2.3 Sleep features of patients

At the multivariate analysis in the group of patients, to evaluate the influence of specific epilepsy-related variables on sleep disorders, the presence of sleep EEG abnormalities was associated with the presence of a recorded sleep disorder (OR=14.8; 95%CI=1.2-175.5; p=0.03) (Table 14) and DoA (OR=12.1; 95%CI=1-146; p=0.05) (Table 15); neck myoclonus was associated with the presence of drug resistance at the last follow-up (OR=19.6; 95%CI= 1.6-231.1; p= 0.02). No association has been found between sleep disorders and a specific IGE syndrome.

3.2.4 Effect of ASMs on sleep disorders

In the subgroup of patients taking ASMs (62.8%) (mean age 34.1 ± 13.4 years, 31.8% men), no association was found between each different ASM used and the sleep disorders recorded, after adjusting for age and sex.

Table 14: Multivariate analysis in patients according to the presence of recorded sleep disorder.

	SD+ n=29	**SD- n=6**	**Univariate analysis**			**Multivariate analysis**		
			OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	39.3±4.9	26.6±2.3	0.9	0.8-0.9	**0.04**	0.9	0.8-0.9	**0.03**
Sex (men) (%)	10 (34.5)	1 (16.7)	0.4	0.04-3.7	0.40	0.2	0.01-3.1	0.23
EEG abnormalities in sleep (%)	25 (86.2)	3 (50)	6.2	0.9-42.5	0.06	14.8	1.2-175.5	**0.03**
Treatment (%)								
ASM	17 (58.6)	5 (83.3)	0.3	0.03-2.7	0.28			
Benzodiazepines	3 (10.3)	3 (21.4)	0.6	0.05-6.7	0.66			
Antidepressants	1 (4.8)	1 (16.7)	0.1	0.02-1.4	0.09			
Seizure freedom (%)	11 (42.3)	2 (50)	0.7	0.09-6.0	0.77			
Drug resistance (%)	9 (34.6)	1 (25)	1.6	0.1-17.6	0.71			

N, number; SD, standard deviation; CI, confidence intervals; OR, odds ratio; ASMs, antiseizure medications; SD, sleep disorder.

Table 15: Multivariate analysis in patients according to the presence of recorded DoA.

	DoA+ n=21	**DoA- n=14**	**Univariate analysis**			**Multivariate analysis**		
			OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (mean ± SD)	21.3±6.8	33.6±11.8	0.9	0.8-0.9	**0.02**	0.9	0.9-1.0	0.15
Sex (men) (%)	8 (38.1)	3 (21.4)	0.4	0.1-2.1	0.30	0.2	0.02-1.9	0.18
EEG abnormalities in sleep (%)	18 (85.7)	10 (71.4)	2.4	0.4-12.9	0.31	12.1	1-146	**0.05**
Treatment (%)								
ASM	10 (47.6)	12 (85.7)	0.1	0.03-0.8	**0.03**			
Benzodiazepines	1 (4.7)	3 (21.4)	0.2	0.01-1.9	0.16	0.7	0.1-3.9	0.67
Antidepressants	1 (4.8)	3 (21.4)	0.2	0.02-1.9	0.16			
Seizure freedom (%)	9 (42.8)	4 (28.6)	2	0.4-9.1	0.37			
Drug resistance (%)	4 (22.2)	6 (50)	0.3	0.06-1.4	0.12	0.1	0.01-1.0	0.051

N, number; SD, standard deviation; CI, confidence intervals; OR, odds ratio; ASMs, antiseizure medications; DoA, disorders of arousal.

3.2.5 Sleep disorders in the subgroup of JME patients

Considering only the subgroup of 19 (54.3%) patients with JME (Table 16), we found significant macrostructural differences with controls, with a significant higher sleep latency (28.5±24.5 vs 12.6±12.9; p=0.001) and lower REM percentage (17.7±5.1 vs 21.1±5.2; p=0.02). As regard to sleep disorders, the findings were comparable with the ones of the whole group of IGE patients, with a significant higher percentage of recorded sleep disorders among JME patients (78.9% vs 50%), as shown in table 17.

Table 16: Demographic and clinical features of the subgroup of patients with JME.

Variables N (%)	**Patients n=19**
Age (mean ± SD)	27.3 ± 11.8
Sex (men) (%)	5 (26.3)
Age at seizure onset (years) (mean ± SD)	15.9 ± 3.7
Family history of epilepsy (%)	7 (36.8)
Abnormal MRI (%)	4/18 (22.2)
Status epilepticus in the history (%)	1 (5.3)
Treatment during the recording	
· ASMs (%)	9 (43.4)
· Antidepressants (%)	2 (10.5)
· Benzodiazepines (%)	1 (5.3)
Drug resistance (%)	4/17 (23.5)
Seizure freedom at the last follow-up (%)	9 (47.4)
ASMs taken by the patients	
Clonazepam (%)	1 (5.3)
Levetiracetam (%)	4 (21)
Lamotrigine (%)	3 (15.8)
Phenobarbital (%)	1 (5.3)
Topiramate (%)	1 (5.3)
Valproate (%)	6 (31.6)

N, number; SD, standard deviation; MRI, magnetic resonance imaging; ASMs, antiseizure medications.

Table 17: Sleep disorders recorded in the subgroup of JME patients and controls.

Sleep parameters	Patients n=35	Controls n=56	p
Disorders of arousal, n (%)	11 (57.9)	17 (30.4)	**0.03**
Rem Behavior Disorder (%)	0	0	/
Periodic Limb Movements, n (%)	2 (10.5)	3 (5.4)	0.43
Bruxism, n (%)	4 (21)	3 (5.4)	**0.04**
Alternating leg muscle activation, n (%)	3 (15.8)	9 (16.1)	0.98
Excessive fragmentary myoclonus, n (%)	0	2 (3.6)	0.40
Neck myoclonus, n (%)	6 (31.6)	3 (5.4)	**0.002**

Values in bold are those statistically significant.

4. Discussion

4.1 Focal epilepsy

Acknowledging the strict relationship between epilepsy and sleep is of outstanding importance in order to ensure an optimal seizures control, also through the management of potentially treatable comorbidities such as sleep disorders.

The most important finding of our study was the significant higher frequency of sleep disorders recorded among patients with epilepsy as compared to normal controls. This finding is not surprising since many previous studies showed that epilepsy is associated with an increase in subjective sleep-related complaints, such as excessive daytime sleepiness, insomnia and poor sleep quality [14] as well as objective evidences of altered sleep architecture [14] with a consequent impact on seizures control and quality of life of patients with epilepsy. However, not all the considered sleep disorders have been found to be more frequent in patients with epilepsy and each of them seem to disclose peculiar features.

Regarding NREM parasomnias, it is well known that they are common in childhood, being present in up to 80% of preschool-age children [72], with a significant association with epilepsy found in many studies [46]. In adults, the lifetime prevalence of various parasomnia ranges from 4% to 67% [73]. It seems that, the presence of DoA in patients with epilepsy may reflect the destabilizing effect of epileptiform activity on sleep stability leading to a greater tendency to

arousals and arousal disorders [5]. The previous studies found an increased prevalence of DoA, especially in patients with mesial temporal lobe epilepsy or SHE [8,31,35,48] In particular, NREM arousal disorders were reported to be more frequent in SHE, being present in the personal history of about 34% of SHE patients, in accordance with the theory for which the two phenomena share a common pathophysiological substrate [49,50,74]. In our sample we only found a positive association between DoA and younger age as described in the general population [73].

However, being a retrospective study, we were not able to reconstruct the anamnestic data of DoA in childhood and we could only rely on PSG findings which are rarely able to record the more complex behaviors of DoA, especially in adults [75]. For this reason, we mostly recorded simple arousal movements (SAM), which have been reported as the most frequently reported patterns in adult patients [76].

Regarding sleep-related movement disorders, except for PLM which has been extensively studied, the other disorders have been poorly investigated in relation with epilepsy [32].

PLM and RLS prevalence among epilepsy patients varies between 10% and 33% in different studies [57,77] with values comparable with our case series (20%). In our sample we found a significant association of PLM with epilepsy and, in patients with epilepsy we found a significant negative association between PLM and drug resistance, indicating that the presence of PLM could be a marker of better outcome

at the last follow-up visit. Moreover, patients with PLM had significantly less seizures in sleep than others. All these data suggest that patients with focal epilepsy and PLM could have a more benign phenotype. This could be maybe due to the beneficial impact of the use of dopaminergic agents [78] or iron replacement therapy on sleep stability [79] of these patients leading to a better seizure control. Moreover, the protective effect of levetiracetam on PLM that we found in our population has been already described in other case series [80] but not confirmed by a subsequent metanalysis [81]. The positive association of topiramate use with PLM has been reported only in one case report, in a patient affected by focal epilepsy [82].

Bruxism is a quite common sleep disorder, but its link with epilepsy has not been specifically explored. In a questionnaire-based study about sleep disorders in patients with epilepsy, the frequency of bruxism in patients was of 10%, but higher in controls, in which it was of 19% [36]. Some other studies report a lower prevalence, of about 8%, in the general population [37]. In our study we found a significant higher prevalence in patients (20%) than controls (4.8%). However, it should be underlined that patients with mesial temporal lobe epilepsy have been reported to have minor motor events during sleep [16]. Among these, oroalimentary automatisms were significantly more frequent than in healthy controls [16], with a pattern that can be similar to chewing movements, thus resembling bruxism. Nonetheless, in our sample, bruxism was equally distributed in all types of epilepsy.

Physiological sleep variants are controversial phenomena which are frequently overlooked by physicians or misinterpreted by researchers, thus usually considered not clinically relevant entities. Some of them, such as NM, are not even included in the ICSD3. This leads to the fact that little is known about their prevalence and significance [68]. ALMA was present in 17% of our patients with epilepsy and 14.5% of controls, with no significant differences. In a previous study a frequency of 33% was found among healthy controls investigated with polysomnography [83] but the authors considered all high frequency leg movements, comprising not only ALMA but also hypnagogic foot tremor. However, even its frequency is comparable in patients and controls, its significant association with the phenotype of SHE, in which was present in 50% of subjects, opens to an intriguing pathophysiological hypothesis: the disinhibition of innate motor behaviors due to the activation of the so-called 'central pattern generators, can produce stereotypical rhythmic motor sequences such as ambulatory behaviours, or bipedal activity, as the one found in ALMA, both in patients and healthy subjects [84,85].

Neck myoclonus is a quite new sleep related motor phenomenon firstly described as a “short stripe-shaped movement-induced artifact” visible vertically over the polysomnographic traces [56]. It has been initially considered as a physiological phenomenon [56] since it was found in 35% to 54.6% of normal subjects undergoing PSG [56,57]. Following reports confirmed NM as an incidental finding in routine VPSG, but with a negative impact on sleep, possibly through sleep

fragmentation [86]. However, up to now, no studies exist on the presence of NM in patients with focal epilepsy. The higher prevalence found in our patients compared to controls, could be possibly explained as an epiphenomenon of sleep instability with frequent arousals that can lead to the most frequent appearance of physiological sleep events. Indeed, in our patients group, the quality of sleep was significantly lower than controls, with significant less TST, longer SL, more N1 light sleep and less REM sleep, possibly due to both the sleep alterations of epilepsy itself and the use of AEDs [10]. Nonetheless, our findings add new insights in the pathogenesis of NM and give a drive to new research on the subject.

Finally, the prevalence of EFM in our study population, both patients and controls, was lower than the prevalence found in the general population (9%) [68] in a VPSG study where it was confirmed its age-dependent association, with the highest values in the group of subjects older than 60 years [57].

Our study certainly has some limitations. In particular, due to its the retrospective nature, we were not able to give accurate anamnestic data on previously reported sleep disorders in our patients, which is a limit in the interpretation of our results. However, we excluded patients and controls with a current sleep complaint at the time of the recording, in order to avoid a selection bias. Moreover, being retrospective, the datum on drug resistance is not sufficiently accurate to give conclusive evidences.

The choice of excluding patients with sleep apnea from the entire study population, which can be a possible limit of our study, has been made to leave out the well-known influence of apneas on sleep stability and on the comorbidities with other sleep disorders, which could have biased our results [87,88].

Moreover, even if large, our sample could have not been sufficient to disclose significant differences in the two groups.

Nevertheless, this is the largest study so far evaluating together parasomnias, sleep-related movement disorder and physiological sleep variants in patients with focal epilepsy and controls by means of PSG recordings.

4.2 Idiopathic Generalized Epilepsy

Sleep disturbances are common among patients with epilepsy [10] and can be secondary to many concurrent causes such as ASMs use or nocturnal seizures. In our study we found a significantly higher frequency of sleep disorders in patients with IGE as compared to controls without epilepsy, by means of nocturnal polysomnography. Moreover, we found a positive association between the recording of a sleep disorder and the presence of sleep EEG abnormalities in patients, supporting the hypothesis that, especially in IGE, sleep disturbances may reflect the intrinsic destabilizing effect of epileptiform activity on the mechanisms

underlying sleep stability [25]. In this regard, the most important finding of our study was the significant higher frequency of DoA among patients with IGE.

DoA from NREM sleep are characterized by an impaired sleep–wake transition [89] and the presence of mixed characteristics of wakefulness and N3 slow wave sleep [90]. Different studies found an increased prevalence of DoA mainly in patients with focal epilepsy, such as mesial temporal lobe epilepsy and SHE [8,31,48] while our previous study did not confirm this evidence [91]. The results of our study are confirmed by previous evidences of a higher prevalence of arousal disorders among children with IGE compared with siblings and healthy controls, using sleep questionnaires [8]. However, it should be underlined that, in our study, we considered as polygraphic evidence of DoA the presence of a dissociation EEG pattern associated with muscular artifact or a motor behavior [66]. This pattern, except for the presence of simple or complex motor episodes, overlaps with the A1 cycling alternating pattern (CAP) subtype occurring in stage N3, which is characterized by delta bursts lasting about 10 seconds combined with mild modifications of the ongoing polygraphic parameters such as muscle tone and heart rate [92]. Not surprisingly, it is widely known that A1 CAP phases have been found to be significantly increased in patients with IGE [92].

Indeed, as already disclosed in previous studies [25] we found a predominance of EEG epileptiform activity during NREM sleep in patients and a significant association between generalized epileptiform discharges and arousal disorders [93].

Therefore, a possible explanation for the higher frequency of DoA among patients with IGE can be the destabilizing effect of epileptiform activity on sleep, leading to a greater tendency to arousals and arousal disorders [1,5,6,94,95]. On the other hand, it has been hypothesized that "arousing stimuli represent an important mechanism in the precipitation of epileptic discharges" [96], so that in IGE enforced arousals during sleep can produce increases in interictal epileptiform discharges [19]. Studies of the CAP in sleep, performed in generalized epilepsies, seem to confirm our speculation suggesting a bidirectional influence of the interictal discharges on arousability and of arousals on the activation of EEG paroxysms [97,98].

Moreover, the comorbidity between generalized epilepsy, namely JME, and DoA, has already been described in two different case reports, both suggesting the presence of a reciprocal relationship between these two disorders [95]. Finally, a very recent study raises the possibility that, being the prevalence of DoA higher in individuals with IGE and their relatives, a shared heritability can exist between these disorders [99].

At any rate, our data seem to disclose an intrinsic dysfunction of NREM sleep in IGE patients which could be the basis for its increased tendency to "dissociated sleep" and to manifest DoA. The relatively high frequency of DoA in the control group (30.3%) seems to be in line with some previous literature findings, as it is already known that in a population of healthy sleepers non disturbing forms of sleep

disorders such as parasomnias are common [100], especially in young patients, since the influence of age has been confirmed in our sample.

However, the a priori inclusion of all subjects with a PSG dissociation pattern as DoA, even without a clinical report of the disease, could have possibly led to an overestimation of the prevalence of the disorder. At any rate, in our study this may have impacted the estimates on both cases and controls.

As regard to the higher frequency of bruxism and neck myoclonus found among IGE patients, recent evidences suggest that both sleep disorders are more frequent in an unselected population of people with epilepsy [101] and in a sample of patients with focal epilepsy [91].

In particular, for bruxism a similar frequency has been found in a recent questionnaire-based study (23.7% of patients with epilepsy vs 5.4% of controls)[101]. However, in this study different epilepsy types were considered. In the group of focal epilepsies almost the same frequency was found in a population of 100 patients (20% of patients with epilepsy vs 4.8% of controls) [91] leading to the speculation of bruxism being an epiphenomenon of fragmented sleep.

Neck myoclonus is a recently discovered sleep phenomenon, initially interpreted as a physiological manifestation [56] but with the evidence of a negative impact on sleep quality [86]. In the group of patients with focal epilepsy, we found a higher frequency of NM, and interpreted it as a marker of sleep fragmentation [91].

In this study its higher prevalence among patients with epilepsy has been confirmed and, most importantly, it has been found to be associated with drug resistance at the last follow-up visit in our sample, corroborating the hypothesis of its possible negative influence on sleep, indirectly leading to poor seizures control.

Indeed, the presence of altered sleep has been confirmed in our sample, with the study of sleep architecture in patients with IGE showing a poor sleep quality with a significantly lower TST, longer SL, and less REM sleep, in line with the findings of previous studies [10,21,30,102].

All the findings of the whole IGE group have been confirmed also in the subsample of patients with JME, which represent the most represented group, being the 54.3% of the all sample.

Our study is certainly limited by its retrospective nature and its hospital-based design which could have, on one hand underestimated the presence of sleep complaints and, on the other hand, overestimated the prevalence of sleep disorders, found in a selected and, possibly, more severe population of patients.

At any rate, the findings of our study offer valuable data regarding sleep disorders in adult patients with IGE and appear to support the undertaking of a prospective study with a larger sample size.

5. Conclusions

In our study we explored the presence of sleep disorders and physiological sleep variants in adult patients with focal epilepsy and IGE by means of PSG. The results of our study showed a high frequency of PLM, bruxism and NM in patients with focal epilepsy as compared to controls. In IGE, we found a higher frequency of sleep disorders, especially DoA, bruxism and NM, as compared to controls. Moreover, we disclosed an association between the recording of a sleep disorder, in particular DoA, and the presence of EEG abnormalities during sleep in patients, supporting the hypothesis of a reciprocal relationship between epileptiform activity and sleep disturbances in IGE.

The presence of sleep disorders in patients with epilepsy could be overlooked, with a possible negative impact on the clinical management of these patients. However, further prospective studies are needed to confirm our findings and to shed light on their significance.

6. References

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