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ORIGINAL ARTICLE

Sleep architecture in drug-naïve adult patients with epilepsy: Comparison between focal and generalized epilepsy

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Abstract

Objective: Sleep impairment is one of the most common comorbidities affecting people with epilepsy (PWE). The bidirectional relation between epilepsy and sleep has been widely established. Several studies investigated subjective sleep quality and daytime vigilance in PWE, highlighting frequent complaints of sleep fragmentation, difficulties in falling asleep, and daytime sleepiness. The present study aimed to evaluate sleep structure in drug-naive PWE, distributed on the basis of epilepsy type, and compared with controls.

Methods: This observational study included adult patients newly diagnosed with epilepsy and drug-naive as well as a control group of healthy subjects. All PWE and controls underwent a dynamic 24-h EEG with signals for sleep recording to evaluate sleep architecture, structure, continuity, and fragmentation.

Results: Twenty-four PWE were included and distributed in two groups based on epilepsy type. Eleven patients were included in the generalized epilepsy group (63.6% male; 34.91 ± 9.80 years) and 13 patients in the focal epilepsy group (53.8% male; 38.69 ± 12.74 years). The control group included 16 subjects (56.3% male; 32.75 ± 12.19 years). Patients with generalized or focal epilepsy had a significantly lower sleep efficiency than controls. Moreover, both patient groups presented the alteration of markers of sleep fragmentation and loss of continuity, with higher indices of sleep stage transitions and arousal. Finally, the two patient groups presented less REM sleep than controls.

Significance: This study highlighted the alteration of sleep quality, continuity, and stability in both patients with focal or generalized epilepsy compared with controls, also in the absence of ictal events. This sleep impairment resulted in the reduction of REM sleep. Therefore, these findings may be explained by the increase in awakenings and sleep stage shifts, which may be attributed to both

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sleep networks impairment and neurotransmission dysfunction in PWE, and also possibly triggered by paroxysmal interictal abnormalities.

KEYWORDS

polysomnography, sleep continuity, sleep fragmentation, sleep impairment, sleep structure

1 | INTRODUCTION

Epilepsy is a common neurological disorder and its worldwide prevalence is around 1% among paediatric, adult and elderly populations.[1] Several comorbidities may affect people with epilepsy (PWE), and sleep impairment is one of the most common complaint of PWE.[2] Besides the well-recognized crucial role of sleep for an healthy life, the bidirectional relation between epilepsy and sleep has been also widely established.[3] On the one hand, sleep presents a critical role for maintaining brain networks efficiency, and sleep deprivation or impairment is associated with a reduced epileptic threshold.[4–6] Moreover, arousals during sleep can increase the possibility to trigger epileptic events owing to dysregulation in electrophysiological oscillations.[7] On the other hand, several studies investigated subjective sleep quality and daytime vigilance in PWE, evidencing frequent complaints of sleep fragmentation, difficulties in falling asleep, and daytime sleepiness.[8–10] Consistently, sleep disorders, such as obstructive sleep apnea and insomnia represent common comorbidities in PWE, which highlights the need for appropriate treatments for concomitantly improving sleep impairment and epilepsy.[11,12] Although there is a general agreement about the importance of studying sleep, a recent review revealed the paucity of studies evaluating sleep architecture in PWE. Specifically, previous studies, mainly focused on assessing sleep structure in patients with generalized epilepsy (GE), documented a reduction of both Non-REM and REM sleep[13–15] and an increase of wake after sleep onset (WASO) in GE patients when compared with control populations.[13,14] Conversely, a decrease in REM sleep and an increase of WASO were evident in patients with focal epilepsy (FE) when compared with controls[16–18]; whereas controversial results about either the decrease or the increase of stage 3 of Non-REM sleep (N3) were reported.[17,18] These previous studies included heterogeneous populations of PWE, frequently treated by anti-seizure medications (ASMs), and presented several methodological differences limiting the comparison between studies and thus preventing to drive definite conclusions about sleep structure in PWE.

Taking into consideration the importance of investigating sleep architecture in PWE and that there is a knowledge gap regarding how epileptic networks can impact sleep, the present controlled study firstly aimed at evaluating sleep structure in PWE, distributed on the basis of epilepsy type, before starting anti-seizure treatment and far from epileptic seizures.

Key Points

- This study analyzed sleep architecture in drug-naïve patients with focal or generalized epilepsy compared with a control group.
- Sleep fragmentation is present in patients with epilepsy also far from epileptic seizures.
- Patients with epilepsy show sleep instability with frequent sleep stage shifts and lower REM sleep than controls.

2 | METHODS

2.1 | Participants and study design

This is a retrospective observational study including PWE admitted at the Epilepsy Center of the University Hospital of Rome "Tor Vergata." Epilepsy was diagnosed and seizures were classified according to the guidelines of the International League Against Epilepsy (ILAE).[19] For this study, only patients who underwent a 24-h ambulatory EEG recording coupled with signals for sleep recording (two electrooculographic channels and the mentalis electromyographic channel) were included. Inclusion criteria for PWE were absence of seizures in the 24 h before the recording, and absence of ictal events during the 24-h recording; no diagnosis of neurologic, psychiatric, or medical disorders other than epilepsy. Exclusion criteria for PWE were treatment with ASMs; the presence of depression, anxiety and post-traumatic stress disorder, evaluated by a clinical interview and validated questionnaires; any suspected sleep disorder (including obstructive sleep apnea syndrome, restless legs syndrome, insomnia, periodic limb movement disorder) investigated by a sleep-medicine interview based on the International Classification of Sleep Disorders (ICSD-3).[20] A group of controls was also recruited at the University Hospital of Rome "Tor Vergata." Specifically, the control

group included outpatients undergoing clinical neurologic screening and a 24-h EEG recording (coupled with signals for sleep recording) for suspected neurological disorders (i.e., sleep disorders or epilepsy), which were ruled out after diagnostic assessments. The control group was similar in age and sex to patients' group. The exclusion criteria for controls were intake of drugs acting on sleep or CNS; shift work; sleep disorders investigated by a sleep-medicine interview based on the ICSD-3.[20]

The study protocol was considered retrospective and observational according to the STROBE statement by the internal review board of the Ethical Committee of the University Hospital of Rome "Tor Vergata".

2.2 | 24-h EEG recording

Patients and controls underwent 24-h ambulatory EEG recording counting also channels for sleep analysis (two electrooculographic channels and the mentalis electromyographic channel) to evaluate nocturnal sleep (Somnomedics, Somnoscreen, SOMNOmedics GmbH-Randersacker, Germany). The signal was stored on a flash card using a common average reference and a time constant of 0.3 s. Electrodes were positioned according to the 10–20 International System.

Sleep analysis was performed according to the standard criteria.[21] The following standard parameters were computed: time in bed (TIB, time spent in bed between lights off and lights on), sleep onset latency (SL, the time-interval between the lights off and the first sleep epoch), total sleep time (TST, the actual sleep time without SL and awakenings), sleep efficiency (SE, the ratio between TST and TIB), REM sleep latency (LREM, the time-interval between the sleep onset and the first epoch of REM), stage 1 of non-REM sleep (N1), stage 2 of non-REM sleep (N2), N3, REM sleep (REM), and WASO. The percentages of the sleep stages and then the sleep stage shift index (the number of sleep stage changes per hour of sleep) were calculated over TST.

The wake bouts, continuous sequences of wake epochs occurring after the beginning of persistent sleep, were identified and computed over TIB in the wake bouts. Blinded researchers (CL, CC, CL) scored the PSG recordings based on the international standard criteria of the American Academy of Sleep Medicine.[21]

2.3 | Statistical analysis

First, descriptive statistics were computed to characterize the sample in terms of sex, age, epilepsy type, seizure type, and seizure frequency. The normality of the data was assessed through the Shapiro–Wilk test.[22] Kruskal-Wallis tests were used to assess the statistical significance of differences in demographic, clinical, and polysomnographic data between patients with FE, patients with GE, and controls. Kruskal-Wallis test is a rank-based procedure that is more appropriate with not-normally distributed data. *P*-value was set at $P < 0.05$ for statistical significance. The statistical analysis was performed using commercial software SPSS version 25.[23]

3 | RESULTS

3.1 | Demographical and clinical data

A total of 24 PWE, with a mean age of 35.96 ± 10.72 years old, was included in the study. Among these patients, 11 (60.53%) had GE (63.6% male; 34.91 ± 9.80 years), and 13 (39.47%) FE (53.8% male; 38.69 ± 12.74 years). The control group included 16 subjects (56.3% male), with a mean age of 32.75 ± 12.18 years old. No differences were found between both groups of PWE and controls regarding sex ($P = 0.882$) and age ($P = 0.301$) (Table 1). Patients with GE did not differ from patients with FE in terms of demographic and clinical features (Table 1).

3.2 | Sleep data

Sleep polysomnographic measures revealed that both groups of patients affected by generalized or focal epilepsy had a significantly lower SE than controls ($P = 0.015$ and 0.016, respectively, Figure 1A), but did not differ from each other. Moreover, patients with FE had a higher percentage of N2 ($P = 0.014$, Figure 1B) and WASO ($P = 0.049$, Figure 1C) than controls, whereas no significant differences were found between patients with GE and controls. A significant difference was initially found in the percentage of REM stage between the three groups ($P = 0.047$, Figure 1D), however, the post hoc analysis did not reach statistical significance, although both patients' groups presented a lower median REM sleep percentage when compared with the control group. Sleep stage shift index was significantly higher in the FE when compared with the control group, and GE patients showed also a trend to have a higher sleep stage shift index than controls, however without reaching statistical significance in the post hoc analysis. Regarding wake bouts, FE patients showed a significant higher number of wake bouts than controls, and GE patients also showed a trend to present higher wake bouts, although not reaching the statistical significance in the post hoc analysis. No differences were found between

TABLE 1 Participants' demographic and clinical features

	Patients with generalized epilepsy ($n = 11$)	Patients with focal epilepsy ($n = 13$)	Controls ($n = 16$)	*P*-value
Median Age, years (Range)	36.00 (21–48)	40.00 (19–56)	33.50 (18–61)	0.301
Gender, *n* (%)				0.882
Male	7 (63.6%)	7 (53.8%)	9 (56.2%)	
Female	4 (36.4%)	6 (46.2%)	7 (33.8%)	
Etiology of Epilepsy, *n* (%)			NA	0.278
Structural	0%	3 (23.1%)		
Unknown	11 (100%)	10 (76.9%)		
Seizure type, *n* (%)			NA	NA
Generalized	11 (100%)	1 (7.7%)		
Focal	0	2 (15.4%)		
Focal and Generalized	0	10 (76.9%)		
Number of seizures in the last 30 days	1.11 ± 0.60	0.85 ± 0.56	NA	NA
Frequency of seizures			NA	NA
<1 per year	6 (54.5%)	8 (61.5%)		
<1 per month	0 (0.0%)	3 (23.1%)		
>1 per month	2 (18.2%)	1 (7.7%)		
>1 per week	1 (9.1%)	1 (7.7%)		

Abbreviation: NA, non-applied.

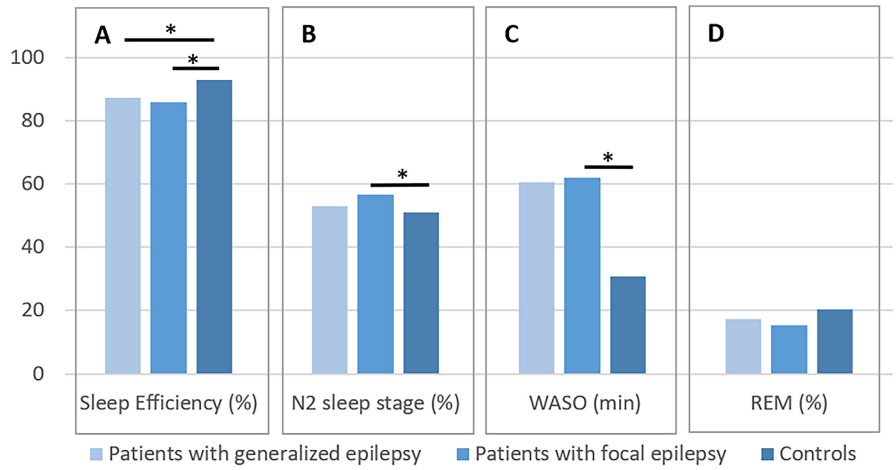

FIGURE 1 Sleep differences between patients with generalized epilepsy, focal epilepsy, and controls. (A) the graphic shows that both groups of patients with epilepsy (generalized or focal) had a significantly lower sleep efficiency index than controls but did not differ from each other. (B) the graphic illustrates the percentage of stage 2 of non-REM sleep (N2) stage, showing that patients with focal epilepsy had a higher percentage of N2 than controls. (C) the graphic shows the duration (in minutes) of wake after sleep onset (WASO) across the three groups, highlighting that patients with focal epilepsy had higher WASO than controls. (D) the plot illustrates the percentage of rapid eye movement (REM) sleep stage in the three groups (no statistical significance was reached with post hoc analysis).

sleep stage shift index and wake bouts between GE and FE groups (Table 2 and Figure 2). Finally, there were no statistically significant differences in the other PSG parameters between the three groups (Table 2). To comprehensively show the sleep architecture pattern in patients with GE or FE, the hypnograms of two emblematic patients are shown in the Figure 3. The representative patients, one for each group, were selected according to the median values of the sleep parameters of the two patients group.

TABLE 2 Polysomnographic data of epilepsy patients and controls

	Patients with generalized epilepsy ($n = 11$)		Patients with focal epilepsy ($n = 13$)		Control group ($n = 16$)		Kruskal-Wallis test		Post hoc analysis		
									GE vs FE	GE vs CG	FE vs CG
	Median	Range	Median	Range	Median	Range	$\chi 2$	*P*-value	*P*-value	*P*-value	*P*-value
TIB (min)	485.25	285.31–515.04	472.57	387.35–602.12	471.78	375.55–605.12	0.181	0.913			
TST (min)	396.30	160.00–453.30	353.00	311.30–566.28	442.75	351.50–558.00	4.485	0.106			
SE (%)	87.20	49.10–94-50	86.00	69.00–94.00	93.05	74.7–97.5	11.002	0.004[ab]	1.000	0.015	0.016
SL (min)	11.30	0.40–23.60	8.90	0.30–28.20	6.05	0.80–35.30	2.026	0.315			
REML (min)	91.00	16.40–221.50	112.50	47.0–280.00	94.25	56.5–269.50	0.969	0.613			
Percentage of REM	17.20	1.40–21.50	15.50	3.20–23.70	20.40	9.10–33.00	6.110	0.047	1.000	0.077	0.165
Percentage of N1	6.40	1.40–18.10	4.80	1.00–13.50	3.90	1.00–9.10	3.159	0.206			
Percentage of N2	53.00	50.60–63.00	56.80	42.20–75.90	51.00	39.6–62.10	8.270	0.016[a]	1.000	0.261	0.014
Percentage of N3	21.60	15.80–33.40	21.30	0.00–33.10	24.25	16.20–35.80	2.348	0.309			
WASO (min)	60.57	7.70–166.05	62.13	35.32–147.59	30.72	11.51–160.03	6.325	0.042[a]	1.000	0.256	0.049
Sleep Stage Shift Index	15.40	5.40–18.70	16.00	9.40–30.40	9.70	2.50–18.70	11.69	0.004[a]	1.000	0.091	0.004
Wake bouts	30.00	7.00–43.00	28.00	18.00–71.00	16.00	1.00–36.00	10.46	0.005[a]	1.000	0.059	0.008

Abbreviations: CG, control group; FE, focal epilepsy; GE, generalized epilepsy; N1, Stage 1 of Non-REM Sleep; N2, Stage 2 of Non-REM Sleep; N3, Stage 3 of Non-REM Sleep; REML, REM latency; SE, sleep efficiency; SL, sleep latency; TIB, total time in bed; TST, total sleep time; WASO, wake after sleep onset.

[a]Significant differences between patients with focal epilepsy and controls.

[b]Significant differences between patients with generalized epilepsy and controls.

4 | DISCUSSION

The findings of the present study support the evidence of sleep architecture impairment in both FE and GE, with the alteration of sleep stability and continuity when compared with controls. Considering both patient groups, patients with FE presented a more dysregulated sleep structure, since N2 and WASO were increased in these patients when compared with controls. Moreover, PWE tended to show the reduction of REM sleep compared with controls, although the difference was not evident in the subgroups' comparison. Hence, these findings emphasize a sleep alteration in PWE, as demonstrated in previous studies.[24] It is noteworthy that current data was achieved in drug-naïve patients and sleep was recorded at least 24-h after ictal events to prove that sleep architecture impairment is present in PWE due to both a possible dysregulation of sleep networks and interictal events, other than seizures and ASMs that can further impair sleep in PWE.

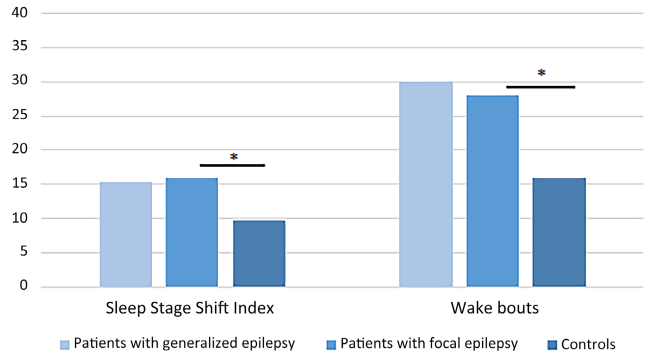

FIGURE 2 Sleep continuity and stability differences between patients with generalized epilepsy, focal epilepsy (FE) and controls. The plot shows that FE patients have a significantly higher sleep stage shift index and a higher number of wake bouts compared with the control group.

The present findings thus reinforce the hypothesis that sleep networks are impaired in PWE, and that epilepsy is associated with alterations of sleep ultradian cycling since the increased fragmentation of sleep, with frequent arousals, wake bouts and sleep stage shifts.[25] These findings indeed show that sleep consolidation and continuity are mainly impaired in PWE, and may also reduce REM sleep. It has been widely shown that REM sleep presents an anticonvulsant effect since epileptic discharges propagation are frequently suppressed during this sleep stage.[26,27] Consistently, REM sleep deprivation can increase ictal and interictal spiking, which may raise the risk of epileptic seizures.[28,29] Consequently, non-REM sleep has been associated with more frequent interictal epileptic discharges (IEDs) and seizures than REM sleep.[27,30,31] Therefore, it is conceivable that sleep impairment in PWE with reduced REM sleep and frequent sleep stage shifts can reduce the ictal threshold and trigger epileptic events, which may cause awakenings and further increase sleep fragmentation in a vicious circle. Consistently, PWE frequently show sleep fragmentation due to several nocturnal awakenings and wake bouts, either related to IEDs or not.[32] Notably, both IEDs and epileptic seizures occur more frequently during unstable stages of sleep, characterized by sleep–wake fluctuations and arousals.[33–35]

Although a recent review identified five studies evaluating sleep macrostructure in PWE, a sleep profile in PWE did not emerge, since only one study showed the increase of WASO in patients with refractory temporal lobe epilepsy compared with patients with frontal lobe epilepsy and controls.[36] In agreement with the results of

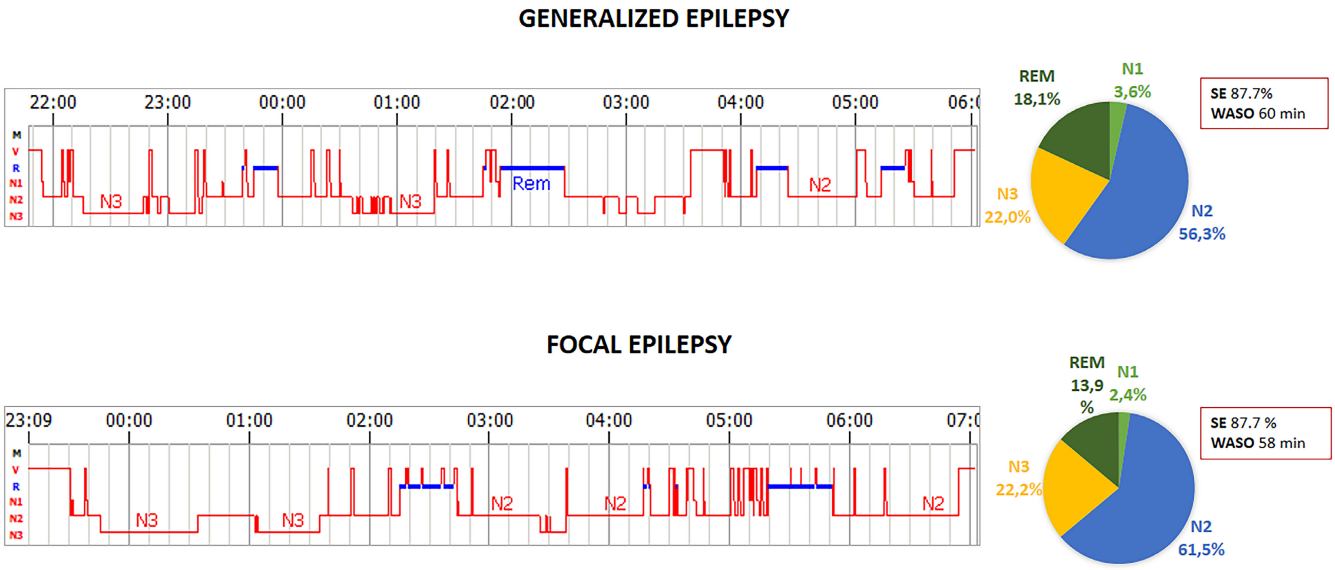

FIGURE 3 Hypnogram of a patient with focal epilepsy and a patient with generalized epilepsy (used as an example of the whole group).

this review, limitations in the previous studies reduced the possibility to deeply investigate sleep architecture in PWE. Specifically, study designs, small patients' samples, and the lack of indices of sleep fragmentation did not allow to better characterize sleep impairment in these patients. Consistently, it appears crucial for clinicians the recognition and targeting of sleep fragmentation in PWE, since the reduction of sleep stage shifts and wake bouts can improve sleep continuity and reduce interictal and ictal events. Hence, the novelty of the present study was the evaluation of sleep architecture in an homogenous group of adult subjects, drug-naïve, and the exclusion of patients with seizures in the 24 h before EEG recording (or showing seizures—either clinical or subclinical—during the recording).

Our results, besides supporting previous findings, underline that sleep impairment in PWE is not only an effect of ASMs[37] or of recent epileptic seizures, but is possibly related to the sleep networks dysregulation.[38] Hence, it is crucial to target sleep impairment, namely, sleep fragmentation, since improving sleep quality may protect against epileptic seizures, reduce the risk of sudden unexpected death, and possibly reduce the burden of comorbidities, such as cognitive deterioration, depression, and anxiety.[39,40]

This study presents some limitations that need to be acknowledged. First, the sample size, although larger than previous reports, does not permit further subgroups' analyses to better define sleep architecture in patients with focal or generalized epilepsy. Moreover, the smaller sample of patients in the GE group did not permit to obtain statistically significant results, but only a clear trend in differentiating GE patients from controls. Further studies should consider assessing sleep structure in larger samples of patients based on epilepsy type and etiology. Second, although the present study showed that epileptic features during sleep are modulated by stage shifts and not by stage amounts or percentages, only a microstructural assessment may disclose additional details on the intrinsic dynamics of the different NREM stages. Future studies should explore these sleep aspects in PWE.

In conclusion, the present study documented the sleep architecture impairment in drug-naïve PWE, highlighting the importance of ensuring sleep quality and continuity in these patients considering that sleep fragmentation and instability can increase the risk of seizures in a vicious cycle. The documentation of sleep alteration in drug-naïve patients further support the hypothesis of sleep networks impairment in epilepsy. Additionally, future researches may also consider the potential clinical use of drugs acting on the nocturnal sleep in PWE given the opportunity to counteract epilepsy by improving sleep.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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