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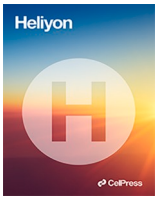

Research article

Duration of N1 sleep is a factor for excessive daytime sleepiness in epilepsy patients with interictal epileptiform discharges: A polysomnographic study

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ABSTRACT

Purpose: This study aimed to identify the occurrence of excessive daytime sleepiness (EDS) in epilepsy patients with interictal epileptiform discharges and to explore the impact of interictal sleep architecture and sleep-related events on EDS.

Methods: This study included 101 epilepsy patients with interictal epileptiform discharges (IED) and 100 control patients who underwent simultaneous polysomnography and video ambulatory electroencephalography for >7 h throughout a single night. Multiple sleep latency tests were used to assess EDS. Comorbid EDS was present in 25 and 11 patients in the IED epilepsy and control groups, respectively. In addition, univariate and multivariate logistic regression analyses were performed to explore the factors influencing EDS.

Results: The epilepsy group had a higher prevalence of comorbid EDS and shorter R sleep duration. Univariate logistic regression analysis indicated that an increased risk of EDS may be associated with prolonged N1 sleep duration, higher arousal index, lower mean saturation (mSaO2), higher oxygen desaturation index (ODI), and duration of wake after sleep onset (WASO). Multivariate logistic regression analysis revealed that N1 sleep duration was significantly correlated with EDS.

Conclusion: In epilepsy patients with IED, the arousal index, mSaO2, ODI, and duration of WASO were weakly correlated with EDS, and the duration of N1 sleep demonstrated a significant positive correlation with EDS, which requires further research.

1. Introduction

The relationship between sleep and epilepsy is complex, and various sleep stages have different effects on epilepsy. Seizures and epileptiform discharges may be promoted during non-rapid eye movement (NREM) sleep, possibly because of the synchronisation of

Abbreviations: EDS, excessive daytime sleepiness; IED, interictal epileptiform discharges; MSLT, multiple sleep latency tests; mSaO2, mean saturation; ODI, oxygen desaturation index; NREM, non-rapid eye movement; REM, rapid eye movement; OSA, obstructive sleep apnoea; PSG, polysomnography; ASM, antiseizure medication; BMI, body mass index; TST, total sleep time; AHI, apnoea-hypopnea index; WASO, wake after sleep onset; PLMI, periodic limb movement index; PLMD, period limb movement disorder; RBD, REM sleep behaviour disorder; IQR, interquartile range; EPV, event per variable.

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neurons between the brainstem, thalamus, and cortex. In contrast, seizures and epileptiform discharges may be inhibited during rapid eye movement (REM) sleep [1]. Excessive daytime sleepiness (EDS) is primarily caused by frequent awakenings and fragmented sleep resulting from electroencephalographic (EEG) changes. Comorbid sleep disturbances are prevalent among patients with epilepsy. Compared with healthy individuals, the risk of EDS, insomnia, and obstructive sleep apnoea (OSA) is 2–3 times higher among patients with epilepsy, which substantially reduces their quality of life [2]. In addition to affecting social and occupational activities in the general population, hypersomnia and general sleep disturbance may exacerbate the condition of patients with epilepsy by accelerating or facilitating key events that complicate and aggravate cognitive and behavioral impairments [3]. Moreover, sleepiness is associated with an increased risk of accidents and imposes a considerable health and economic burden. Therefore, it is essential to identify the factors that influence sleepiness, particularly in patients with epilepsy. The aetiology of EDS in epilepsy is multifaceted, involving psychological distress, epilepsy-related factors, and concurrent sleep disruptions, often associated with undiagnosed sleep disorders [4]. EDS can be assessed using subjective or objective methods. From a subjective point of view, the Epworth Sleepiness Scale (ESS) is the most commonly used tool in sleep research and has been extensively used in most existing studies. However, the most objective and reliable diagnostic criterion for EDS is the multiple sleep latency test (MSLT) [5], although it requires considerable effort and time to complete. Therefore, it is critical to identify specific indicators in the nocturnal polysomnography (PSG) sleep architecture or sleep-related events that reflect the results of the MSLT. Although the relationship between epilepsy and EDS has been previously reported, only few studies have targeted individuals with interictal epileptiform discharges (IED). Excluding the confounding effect of seizures on EDS improves the reliability and robustness. Our study aimed to address these questions by analyzing the sleep structure characteristics of patients with IED and EDS. The factors influencing EDS were investigated using 16-channel video EEG and PSG to understand the distribution of EDS in patients with IED and to provide evidence for the early identification of high-risk groups and complications of EDS in patients with IED epilepsy.

2. Methods

2.1. Research design and objectives

This single-centre retrospective case-control study included a control group and an epilepsy group comprising patients with IED who had undergone 16-channel video EEG, including PSG between July 1, 2018 and October 1, 2022 at the Department of Neurology and Sleep Medicine Centre of Fujian Provincial Governmental Hospital. The study protocol was approved by the Institutional Ethics Committee. Patients who met the following criteria were included in the case group: age $\geq$16 years, with written consent from themselves (and their guardians if necessary) to be included in the study; a diagnosis of epilepsy according to the International League Against Epilepsy 2017 criteria [6]; nighttime sleep monitoring time >7 h; and a diagnosis of IED [7]. The exclusion criteria were as follows: patients with a known history of alcoholism, consumption of coffee and other beverages affecting sleep, intake of other medications affecting sleep (except antiepileptic drugs) in the past 2 weeks; mental disorders, disorders of the circulatory system, or other diseases that affect sleep; those who had epileptic seizures or did not have epileptiform discharges during the monitoring period; those with drug-resistant epilepsy or epilepsy syndrome; those who could not cooperate with the examination; those with incomplete PSG monitoring data; and those lacking MSLT data. The control group consisted of volunteers who visited the Sleep Medicine Centre or the Department of Neurology of Fujian Provincial Governmental Hospital during the same period. The participants were randomly recruited and had no relationship to the epilepsy group. Patients aged $\geq$16 years who provided written consent from themselves (and their guardians if necessary) to be included in the study and underwent nighttime sleep monitoring for >7 h were included in the control group. Patients with a history of alcoholism, consumption of coffee and other caffeinated drinks, intake of drugs that affect sleep in the past 2 weeks; those with mental disorders, disorders of the circulatory system, or other diseases that affect sleep; those who could not cooperate with the examination; those with incomplete PSG data; and those lacking MSLT data were excluded. The demographic data of each patient, including age, sex, body mass index (BMI), sleep structure, sleep progression, sleep-related events, type of seizure, site of epileptic discharge, number of medications taken, and medical history, were recorded.

2.2. PSG parameters

To minimise undesired interference from the surroundings, each patient underwent at least 7 h of PSG (Alice 6 LDxS; Philips) at the sleep medicine centre throughout the night. The monitoring items included EEG (16 leads), electrooculogram (2 leads), electromyogram (EMG) from the submental and peroneal anterior muscles, thoracoabdominal respiration, body position change, leg movement, blood oxygen saturation from the index finger, snoring, oral-nasal airflow, and electrocardiogram. Infrared video was also used to record any seizures or abnormal sleeping behaviour that the patient may have experienced. The outcomes of the PSG test included total sleep time, sleep latency duration, duration of wake after sleep onset (WASO), sleep efficiency, mean saturation (mSaO2), oxygen desaturation index (ODI), arousal index, and apnoea-hypopnea index (AHI), in accordance with the American Academy of Sleep Medicine 2.3 scoring standard. The ODI was defined as the number of desaturations $\geq$3 % per hour of sleep [8]. Based on the AHI, obstructive sleep apnoea (OSA) was graded as follows: Grade 0: AHI <5 events/h; Grade 1: 5 events/h $\leq$ AHI <15 events/h; Grade 2: AHI $\geq$15 events/h [9]. A mean sleep latency of less than 8 min indicated EDS, which was determined using MSLT [10].

2.3. MSLT

The MSLT included five nap experiments, which started 1.5 h after waking up in the morning and were performed separately at 09:00, 11:00, 13:00, 15:00, and 17:00. The setting where the patient lies down should be calm, dark, and at a pleasant temperature. Naps begin with the lights out, signalling the start of sleep. The nap sessions are standardized to 20 min initially, with an extension of 15 min if sleep occurs. Sleep latency duration was defined as the duration from the lights off to the onset of sleep.

2.4. Statistical methods

Continuous variables with a normal distribution are expressed as the mean ± standard deviation (x ± SD), and those without a normal distribution are expressed as the median M (interquartile range P25–P75). Categorical variables are presented as frequencies and percentages. The analysis of differences between groups was performed as follows: *t*-test was used for normally-distributed continuous variables; Wilcoxon rank-sum test was applied for variables with non-normal distribution or ordered categorical variables; chi-squared test, continuity correction chi-squared test, Pearson chi-squared test, or Fisher's exact test were used for comparison of categorical variables between groups. The odds ratios (OR) and 95 % confidence intervals (CI) of the factors influencing EDS in patients with epilepsy and IED were calculated using univariate logistic regression. The variables included in the multivariate logistic regression were based on a combination of univariate logistic regression analysis and the findings of previous studies. All statistical analyses were performed using SPSS software for Windows (version 25.0, IBM Corp., Armonk, NY, USA), and statistical significance was set at $P < 0.05$ in two-tailed statistical tests.

3. Results

Between July 1, 2018 and October 1, 2022, 119 adult patients with epilepsy who had undergone synchronous video PSG and long-term video EEG at Fujian Provincial Governmental Hospital were enrolled in this study. Following the exclusion of nine patients without experimental MSLT data, five with epileptic seizures during the monitoring period, and four with no detectable epileptiform discharges (Fig. 1), 101 patients were included in the final analyses. Thirty patients received monotherapies, including valproic acid (n

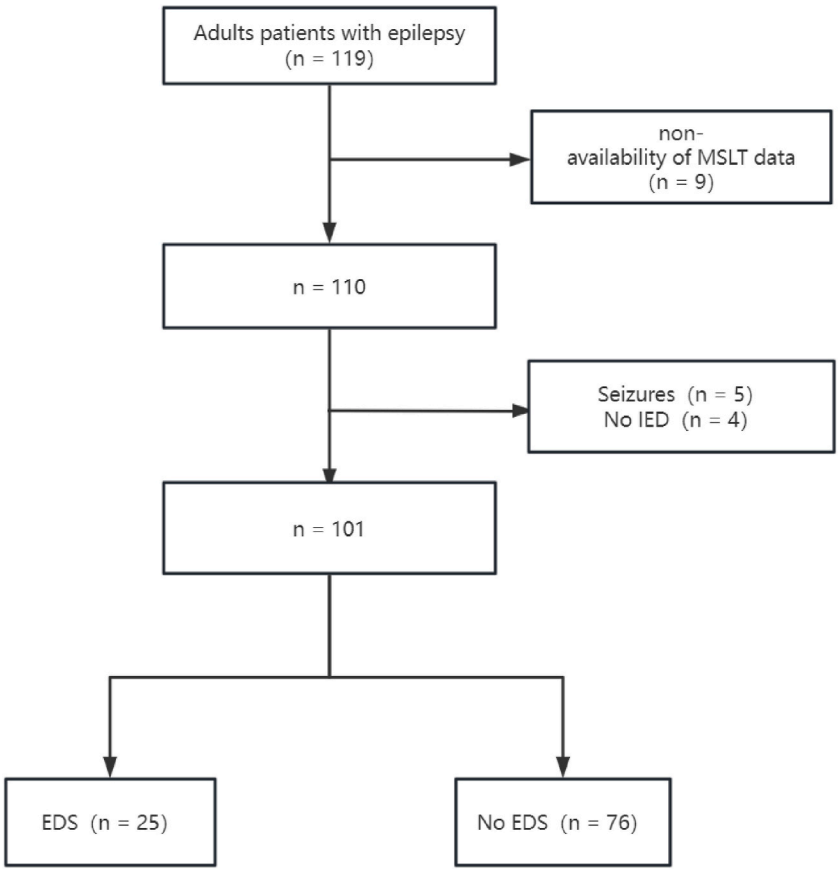

Fig. 1. Flow chart of patient selection process Abbreviations: EDS, excessive daytime sleepiness; IED, interictal epileptiform discharges; MSLT, multiple sleep latency test.

= 10), phenytoin (n = 1), carbamazepine (n = 5), oxcarbazepine (n = 12), and levetiracetam (n = 2). Ten patients were treated with a combination of two anti-seizure medications (ASMs), which included oxcarbazepine + clonazepam (n = 2), valproic acid + levetiracetam (n = 1), valproic acid + gabapentin (n = 1), valproic acid + lamotrigine (n = 2), valproic acid + oxcarbazepine (n = 2), topiramate + clonazepam (n = 1), and topiramate + lamotrigine (n = 1). Three patients received three ASMs, including topiramate + oxcarbazepine + levetiracetam (n = 1), lamotrigine + valproic acid + clonazepam (n = 1), and oxcarbazepine + topiramate + clonazepam (n = 1).

3.1. Participants' characteristics

Table 1 summarises the demographic data of patients in the IED epilepsy and control groups. The differences in the average age 57.0 vs. 62.5 (IQR, 36.0–74.0 years vs. 49.0–71.8 years, $P = 0.347$), BMI 22.60 vs. 22.9 (IQR, 20.60–24.80 kg/m^2 vs. 20.5–25.3 kg/m^2, $P = 0.873$), and proportion of men 58 vs. 44 men (57.4 % vs. 44.0 %, $P = 0.057$) were not statistically significant between the epilepsy and control groups. Compared with the control group, the proportion of patients with hypertension in the epilepsy group was lower (20 [19.8 %] vs. 36 [36.0 %], $P = 0.01$) (Table 1).

3.2. Comparison of sleep architecture and sleep-related events between the epilepsy and control groups

Table 2 summarises the comparison of PSG results between the IED epilepsy and control groups. Compared with the controls, patients in the epilepsy group had a higher incidence of EDS as a comorbid condition (25 [24.8 %] vs. 11 [11.0 %], $P = 0.01$) and shorter R sleep duration ($P = 0.019$).

3.3. Comparison of demographic data and PSG results between EDS and no-EDS groups and the impact of demographic data and PSG results on the incidence of EDS within patients in the epilepsy group

The demographic data and PSG results between the EDS and no-EDS subgroups in the epilepsy group were compared (Table 3). Among the 25 patients with epilepsy and EDS included in the study, 14 were men (56.0 %) and 11 were women (44.0 %). The mean age of the patients in the EDS group was 65.0 (49.0–79.5) years, and the mean course of disease was 2.0 (0.4–9.0) years. Regarding the distribution of epileptic discharge, seven patients (28.0 %) had epileptic discharges originating predominantly from the left hemisphere of the brain. Similarly, seven patients (28.0 %) had epileptic discharges predominantly from the right hemisphere. Bilateral synchronous discharge and bilateral alternating discharge was reported in five (20.0 %) and six (24.0 %) patients, respectively. Most patients (n = 18, 72.0 %) were diagnosed with focal epilepsy, and seven (18.0 %) had generalized epilepsy. Among the 11 patients treated with ASMs, eight received one ASM (carbamazepine, n = 2; oxcarbazepine, n = 2; and valproic acid, n = 4), one received a combination of two ASMs (valproic acid + gabapentin), and two received a combination of three ASMs (lamotrigine + valproic acid + clonazepam and oxcarbazepine + topiramate + clonazepam). Of the 76 patients in the no-EDS group, 44 were men (57.9 %) and 32 were women (42.1 %). The mean age of the patients in the no-EDS group was 55.0 (34.3–69.8) years, and the mean course of disease was 1.0 (0.5–4.75) years. Epileptic discharge from the left and right sides was reported in 24 (31.6 %) and 25, (32.9 %) patients, respectively. Bilateral synchronous discharge and bilateral alternating discharge were observed in 10 (13.2 %) and 17 (22.4 %) patients, respectively. Most patients (n = 50, 65.8 %) were diagnosed with focal epilepsy, and 26 (34.2 %) had generalized epilepsy. ASM use was reported in 36 patients. Among them, 20 patients received monotherapy with one of the following ASMs: levetiracetam (n = 2), oxcarbazepine (n = 10), carbamazepine (n = 3), valproic acid (n = 6), and phenytoin (n = 1); nine patients received combination therapy with two ASMs, including levetiracetam + valproic acid (n = 1), oxcarbazepine + valproic acid (n = 2), oxcarbazepine + clonazepam (n = 2), topiramate + lamotrigine (n = 1), topiramate + clonazepam (n = 1), and lamotrigine + valproic acid (n = 2); and one patient received combination therapy with three ASMs (levetiracetam + oxcarbazepine + topiramate).

The univariate logistic regression analysis demonstrated that the increased risk of EDS may be correlated with the N1 sleep duration

Table 1
Comparison of demographic data between the epilepsy and control groups.

	Epilepsy group (n = 101)	Control group (n = 100)	*P-value*
Age, M (IQR)	57.0 (36.0–74.0)	62.5 (49.0–71.8)	0.347[a]
BMI, M (IQR)	22.60 (20.60–24.80)	22.9 (20.5–25.3)	0.873[a]
Sex			0.057[b]
Male (%)	58 (57.4)	44 (44.0)	
Female (%)	43 (42.6)	56 (56.0)	
Hypertension (%)	20 (19.8)	36 (36.0)	0.01[cb]
Diabetes (%)	11 (10.9)	12 (12.0)	0.805[b]
Cerebrovascular disease (%)	19 (18.8)	14 (14.0)	0.357[b]
Parkinson's disease or cognitive impairment (%)	3 (3.0)	4 (4.0)	0.989[b]

Abbreviations: BMI, Body mass index; IQR, interquartile range.
[a] Wilcoxon rank-sum test.
[b] Chi-square test.
[c] $P < 0.05$.

Table 2
Comparison of polysomnography results between epilepsy and control groups.

	Epilepsy group (n = 101)	Control group (n = 100)	*P-value*
Sleep latency (min), M (IQR)	12.0 (5.5–18.0)	11.5 (5.6–23.5)	0.610[a]
TST (min), M (IQR)	393.0 (347.8–469.8)	409.8 (348.8–454.4)	0.772[a]
R sleep duration (min), M (IQR)	55.0 (36.8–78.5)	71.0 (53.1–86.6)	0.019[ca]
N1 sleep duration (min), M (IQR)	56.0 (42.0–81.8)	52.0 (35.1–79.0)	0.322[a]
N2 sleep duration (min), M (IQR)	233.0 (187.0–285.0)	243.8 (206.6–284.9)	0.345[a]
N3 sleep duration (min), M (IQR)	24.0 (1.0–56.5)	24.8 (7.5–58.0)	0.695[a]
Arousal index, M (IQR)	11.9 (7.5–15.3)	10.5 (6.6–13.3)	0.231[a]
AHI, M (IQR)	10.8 (4.4–28.2)	10.1 (4.2–24.2)	0.464[a]
mSaO2, M (IQR)	94.0 (93.0–96.0)	94.0 (93.3–95.0)	0.558[a]
ODI, M (IQR)	11.0 (4.9–32.4)	10.0 (4.1–24.4)	0.252[a]
Minimum blood oxygen saturation, M (IQR)	86.0 (80.0–90.5)	87.0 (83.0–90.0)	0.212[a]
WASO (min), M (IQR)	95.0 (55.3–146.3)	98.0 (53.3–142.3)	0.726[a]
Sleep efficiency, M (IQR)	81.4 (70.7–90.0)	80.9 (72.3–89.2)	0.675[a]
PLMI, M (IQR)	2.8 (0–15.4)	6.6 (1.0–19.8)	0.072[a]
OSA (%)			0.935[b]
0	27 (26.7)	28 (28.0)	
1	30 (29.7)	31 (31.0)	
2	44 (43.6)	41 (41.0)	
PLMD (%)	26 (25.8)	31 (31.0)	0.408[b]
RBD (%)	8 (7.9)	8 (8.0)	0.983[b]
EDS (%)	25 (24.8)	11 (11.0)	0.010[cb]

Abbreviations: TST, total sleep time; AHI, apnoea-hypopnoea index; mSaO2, mean saturation; ODI, oxygen desaturation index; WASO, wake after sleep onset; PLMI, periodic limb movement index; OSA, obstructive sleep apnoea; PLMD, periodic limb movement disorder; RBD, REM sleep behaviour disorder; EDS, excessive daytime sleepiness; IQR, Interquartile range.

[a] Wilcoxon rank-sum test.

[b] Chi-square test.

[c] $P < 0.05$.

(OR, 1.019; 95 % CI, 1.007–1.031; $P = 0.002$), higher arousal index (OR, 1.048; 95 % CI, 1.004–1.094; $P = 0.033$), lower mSaO2 (OR, 0.771; 95 % CI, 0.620–0.960; $P = 0.020$), higher ODI (OR, 1.026; 95 % CI, 1.006–1.047; $P = 0.011$), and longer duration of WASO (OR, 1.007; 95 % CI, 1.001–1.013; $P = 0.014$).

Impact of N1 sleep duration, arousal index, mSaO2, ODI, and OSA on the incidence of EDS within patients in the epilepsy group.

A multivariate logistic regression model was constructed (Table 4), including predictors such as the duration of N1 sleep, arousal index, mSaO2, ODI, and OSA, which indicated that the duration of N1 sleep had a statistically significant effect on EDS (OR, 1.023; 95 % CI, 1.005–1.041; $P = 0.014$). The variance inflation factor was used to assess variable collinearity among the predictor variables. The accuracy and stability of the models were evaluated using calibration curves and the Hosmer–Lemeshow goodness-of-fit test [3]. The results showed that VIF was less than 5 and tolerance was greater than 0.1, suggesting no significant collinearity. The P-value of the Hosmer–Lemeshow test was 0.697, indicating a high goodness of fit of the model.

4. Discussion

Patients with epilepsy are prone to multiple sleep disorders, among which EDS is the most common, with an incidence rate of 14.5%–49.6 % [11]. In our study, EDS was reported in 24.8 % of patients with epilepsy. In addition, epileptic seizures may interfere with the nocturnal sleep structure and result in EDS [12]. Therefore, we excluded patients who experienced epileptic seizures while monitored at night to better identify the elements affecting EDS. The prevalence of EDS in healthy individuals ranges from 2.5 % to 7 % [13,14], which is lower than the 11.0 % incidence of EDS in the control group in our study. This discrepancy could be attributed to the inclusion of both inpatients and outpatients who visited the department of neurology and the sleep center. Therefore, some patients develop insomnia or other sleep disorders.

Our findings demonstrated that R sleep duration was shorter in patients with epilepsy. Klobucnikova et al. found that the reduced proportion of the R-phase in patients with epilepsy resulted in sleep fragmentation, which mainly contributed to EDS [15]. A reduction in the proportion of stage 3 sleep and stage R sleep was related to poor sleep quality and the occurrence of EDS in patients with epilepsy [16]. Although the results of our study were not statistically significant, the difference in median R sleep duration between the EDS (44.5 [16.5–63.5] min) and no-EDS group (61.3 [38.5–82.6] min) had a *P* value of 0.056 (borderline significance), which could be attributed to the small sample size.

The correlation between OSA and EDS remains conflicting. OSA patients often complain of sleepiness, with an incidence rate of 16%–22 % [17,18]. Regardless of whether the diagnosis of OSA is based on the results of the scale or PSG study, patients with epilepsy and OSA are more likely to experience EDS [15,19], with hypoxaemia, hypercapnia, and slight arousal playing key roles as determinants [20]. In a study that included 40 patients with epilepsy, PSG revealed that sleep-disordered breathing (P = 0.002) and REM sleep duration (P = 0.029) were significantly correlated with Epworth sleepiness scale. In addition, recurrent apnoea episodes can cause sleep fragmentation and a substantial decrease in mSaO2 [21], both of which increase the risk of EDS. Concurrent noninvasive ventilator therapy can effectively lower the risk of EDS [22]. A cross-sectional study of 874 OSA patients from tertiary care centres in

Table 3
Demographic data and PSG results between the EDS and no-EDS groups and univariate logistic regression analysis on the incidence of EDS within patients in the epilepsy group.

			EDS				
	EDS (n = 25)	No-EDS (n = 76)	B	SD	OR	95 % CI	*P*-value
Age, years	65.0 (49.0–79.5)	55.0 (34.3–69.8)	0.017	0.011	1.018	0.996–1.039	0.103
BMI, kg/m^2	23.1 (20.8–24.7)	22.4 (20.5–24.8)	0.034	0.070	1.035	0.902–1.187	0.628
Sex							
Male	14 (56.0)	44 (57.9)					
Female	11 (44.0)	32 (42.1)	−0.077	0.465	0.926	0.372–2.303	0.868
Hypertension	4 (16.0)	16 (21.1)	0.336	0.614	1.400	0.420–4.663	0.584
Diabetes	4 (16.0)	7 (9.2)	0.630	0.675	0.533	0.142–1.998	0.350
Cerebrovascular disease	7 (28.0)	12 (15.8)	0.730	0.545	0.482	0.166–1.404	0.181
Parkinson's disease or cognitive impairment	1 (4.0)	2 (2.6)	0.433	1.247	0.649	0.056–7.473	0.729
Epileptic discharge distribution							
Left side	7 (28.0)	24 (31.6)					
Right side	7 (28.0)	25 (32.9)	−0.191	0.640	0.826	0.236–2.899	0.766
Bilateral synchronous discharge	5 (20.0)	10 (13.2)	−0.232	0.639	0.793	0.227–2.776	0.717
Bilateral alternating discharge	6 (24.0)	17 (22.4)	−0.348	0.725	1.417	0.342–5.866	0.631
Epilepsy types							
Generalized	7 (28.0)	26 (34.2)					
Focal	18 (72.0)	50 (65.8)	−0.291	0.507	0.748	0.277–2.019	0.566
Course of disease	2.0 (0.4–9.0)	1.0 (0.5–4.75)	−0.001	0.031	1.001	0.942–1.063	0.985
IED index	0.6 (0.3–2.1)	0.5 (0.3–1.2)	0.150	0.172	1.162	0.830–1.626	0.382
Receiving ASM	11 (44.0)	32 (42.1)	−0.077	0.465	0.926	0.372–2.303	0.868
Type of ASM therapy							
0	14 (56.0)	44 (57.9)					
1 (Monotherapy)	8 (32.0)	22 (28.9)	−1.838	1.263	0.159	0.013–1.890	0.145
2 (Combination of two ASMs)	1 (4.0)	9 (11.8)	−1.705	1.292	0.182	0.014–2.290	0.187
3 (Combination of three ASMs)	2 (8.0)	1 (1.3)	−2.890	1.616	0.056	0.002–1.319	0.074
Sleep latency (min)	9.50 (5.0–17.0)	12.3 (6.0–19.9)	−0.001	0.012	0.999	0.976–1.023	0.927
TST (min)	405.5 (355.5–481.8)	391.0 (342.4–454.6)	0.002	0.002	1.002	0.997–1.006	0.437
R sleep duration (min)	44.5 (16.5–63.5)	61.3 (38.5–82.6)	−0.014	0.008	0.986	0.971–1.000	0.056
N1 sleep duration (min)	70.5 (49.8–129.0)	53.5 (38.8–75.5)	0.019	0.006	1.019	1.007–1.031	0.002[a]
N2 sleep duration (min)	237.0 (188.5–328.3)	232.8 (186.5–277.6)	0.001	0.003	1.001	0.996–1.007	0.719
N3 sleep duration (min)	16.5 (0.3–60.0)	27.5 (1.1–56.8)	−0.003	0.006	0.997	0.985–1.009	0.617
Arousal index	13.4 (9.1–17.4)	10.8 (7.3–14.4)	0.047	0.022	1.048	1.004–1.094	0.033[a]
AHI	18.5 (7.6–49.6)	10.0 (3.9–24.1)	0.019	0.010	1.020	0.999–1.040	0.058
mSaO2 (%)	94.0 (92.0–95.0)	95.0 (93.3–96.0)	−0.260	0.112	0.771	0.620–0.960	0.020[a]
ODI	24.1 (6.5–55.5)	9.9 (4.5–24.8)	0.026	0.010	1.026	1.006–1.047	0.011[a]
Minimum blood oxygen saturation (%)	81.0 (78.0–86.5)	87.0 (81.3–91.0)	−0.021	0.020	0.980	0.942–1.019	0.303
WASO (min)	112.0 (55.3–230.8)	84.3 (54.9–135.1)	0.007	0.003	1.007	1.001–1.013	0.014[a]
Sleep efficiency	77.6 (63.4–89.7)	81.9 (71.9–90.3)	−0.026	0.016	0.975	0.944–1.006	0.114
PLMI	4.6 (0–18.3)	2.45 (0–15.0)	0.002	0.011	1.002	0.980–1.025	0.865
OSA (%)							
0	3 (12.0)	24 (31.6)					
1	8 (32.0)	22 (28.9)	−1.317	0.693	0.268	0.069–1.041	0.057
2	14 (56.0)	30 (39.5)	−0.249	0.525	0.779	0.279–2.179	0.634
PLMD (%)	7 (28.0)	19 (25.0)	−0.154	0.518	0.857	0.310–2.367	0.766
RBD (%)	3 (12.0)	5 (6.6)	−0.661	0.770	0.516	0.114–2.336	0.391

Abbreviations: BMI, Body mass index; IED, interictal epileptiform discharge; TST, total sleep time; AHI, apnoea-hypopnoea index; mSaO2, mean saturation; ODI, oxygen desaturation index; WASO, wake after sleep onset; PLMI, periodic limb movement index; OSA, obstructive sleep apnoea; PLMD, period limb movement disorder; RBD, REM sleep behaviour disorder; EDS, excessive daytime sleepiness; ASM, anti-seizure medication.
[a] $P < 0.05$.

China showed that AHI and mSaO2 were independent factors for severe EDS (ESS ≥17) in OSA patients [23]. A large multicentre study involving 34,684 patients by Ulander et al. also showed that AHI, ODI, and mSaO2 were associated with EDS; however, ODI was a better predictor of EDS than AHI [24]. Chen et al. showed that the ESS score gradually increased with OSA severity and that ODI was the strongest determinant of the ESS score [25]. However, some studies have suggested that OSA is only weakly associated with daytime sleepiness [26]. Nonetheless, all these studies used the ESS scale for diagnosing EDS, which has subjective limitations. Wu M et al., in their study of 101 patients with narcolepsy, found that N1%, arousal index, and periodic limb movements index were positively associated with objective EDS in the early-onset group (age at disease onset ≤15 years) [27]. Kainulainen et al. analysed the PSG and MSLT results of 362 OSA patients and found that mSaO2 had a significantly stronger negative correlation with the average sleep latency than AHI [28]. Through the investigation of the objective index in MSLT, our study further showed that ODI, mSaO2, and arousal index may be related to EDS, which is consistent with previous studies. The intermittent hypoxia that can be reflected by the ODI may result in chronic sleep fragmentation and sleep deprivation, leading to exacerbation of EDS [29]. The arousal index may lead to repeated activation of the sympathetic nervous system, causing chronic partial sleep deprivation [30], resulting in disruption of sleep continuity and sleep fragmentation [31]. In addition, our findings indicated that WASO may be related to EDS. WASO reflects the

Table 4
Multivariable logistic regression analysis of the presence of co-occurring epilepsy and EDS in patients.

Variables	Multivariable logistic regression analysis				
	B	SD	OR	95 % CI	*P*-value
N1 sleep duration	0.023	0.009	1.023	1.005–1.041	0.014[a]
Arousal index	−0.044	0.039	0.957	0.886–1.033	0.256
mSaO2	−0.117	0.145	0.890	0.670–1.181	0.419
ODI	0.022	0.021	1.022	0.981–1.065	0.299
OSA					
0	1				
1	−0.036	0.972	0.965	0.144–6.488	0.971
2	0.792	0.784	2.208	0.475–10.268	0.312

Abbreviations: mSaO2, mean saturation; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea.
[a] Adjusted for arousal index, mSaO2, ODI, and OSA; $*P < 0.05$.

severity of repeated awakenings at night and affects sleep efficiency; however, available reports demonstrating this association are scarce. In addition, our findings showed that the severity of OSA (e.g., AHI) was not significantly associated with EDS, warranting further exploration of alternative indicators of illness severity, such as ODI and mSaO2, or incorporation of these indicators into the routine evaluation of OSA severity.

The variables included in the multivariate logistic regression were based on a combination of univariate logistic regression and findings from previous studies. Owing to the small sample size, to improve event per variable (EPV), WASO was excluded from the multivariate logistic regression model [32]. Finally, N1 sleep duration, arousal index, mSaO2, ODI, and OSA were incorporated into the multivariate logistic regression model. Our findings demonstrated a significant positive correlation between N1 sleep duration and EDS. N1 sleep is the lightest stage of sleep and begins when more than 50 % of the alpha waves are replaced with low-amplitude mixed-frequency activity, often alternating with brief episodes of awakening. N1 sleep duration is a period of transition from unsynchronised beta and gamma brain waves to more synchronised but slower alpha waves, and then to theta waves with slow-rolling eye movements [33]. Our findings indicated that the longer duration of N1 sleep at night in patients with epilepsy and IED contributes to daytime sleepiness the following day. Although prolonged N1 sleep at night is a risk factor for EDS in patients with epilepsy during the interictal phase, studies analyzing the relationship between N1 sleep duration and EDS are limited. Slonkova et al. [34] reported a significant negative correlation between hypocretin-1/orexin-A and N1 sleep duration. Consistent with this, a study specifically examining different types of central disorders of hypersomnolence in children suggested that instability in N1 sleep duration may be a biological marker of hypocretin-1/orexin-A deficiency [35]. EDS is a clinical manifestation of narcolepsy. Zhang et al. found that WASO, arousal index, and N1% of narcolepsy type 1 (NT1) increased significantly, indicating that NT1, rather than NT2, exhibited shallow and more fragmented sleep [36]. Pizza et al. found that the N1 sleep duration helped confirm clinically suspected NT1 by analysing the nocturnal sleep macrostructure and MSLT of night sleep in different types of central disorders of hypersomnolence [37]. Therefore, we speculated that the relationship between N1 sleep duration and EDS may be related to hypocretin-1/orexin-A levels. Unfortunately, owing to the invasive nature of lumbar puncture, our study lacked data on hypocretin-1/orexin-A levels. Future studies should aim to incorporate hypocretin-1 measurements to provide a more comprehensive analysis of the factors contributing to EDS.

Our study had several limitations. First, this was a single-centre study with a small sample size, and only adult patients with epilepsy receiving outpatient treatments at the sleep medication centre were included, which might have contributed to selection bias. Second, the effect of the type and dosage of ASMs on sleep patterns and sleepiness during the day was not completely eliminated. Valproic acid, oxcarbazepine, carbamazepine, and levetiracetam had no effect on EDS [38,39], whereas topiramate [40] and lamotrigine had a minimal effect on EDS [41]. In addition, clonazepam, phenytoin, and gabapentin may stimulate EDS [40,41]. However, only one patient in our study received phenytoin (no-EDS group) and gabapentin (EDS group), three patients in the no-EDS group received clonazepam, and two patients in the EDS group received clonazepam; therefore, we believe that their influence on the results of the study was negligible. In the future, we will further expand the sample size and conduct multi-center studies to further investigate the effects of different ASM on sleep. Third, the sleep monitoring in our study was limited to a single night. Repeated experiments over two or more nights could enhance the reliability of the data. However, extending the monitoring period increases the resources required, including time and financial costs, and patient cooperation can be challenging. Finally, other potential variables, such as psychiatric conditions, drug interactions, living conditions and more detailed properties of epilepsy could have influenced our findings, warranting further exploration.

5. Conclusion

In conclusion, nocturnal simultaneous 16-channel video electroencephalography, including PSG and next-day MSLT, is an objective method that can be employed in clinical practice for patients with epilepsy and comorbid sleep disorders during the interictal phase. These techniques can be used to determine the characteristics of nocturnal and daytime sleep disturbances. Moreover, the likelihood of experiencing excessive daytime drowsiness increases with an increase in the duration of light sleep (N1) at night. In the future, we can expand the sample size for further validation and try interventions to mitigate EDS.

Ethical standards

The study was approved by the Ethics Committee of Fujian Provincial Governmental Hospital (approval number: 2019J01012090) and was conducted in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments. All the participants provided written informed consent.

Data availability statement

The datasets generated and/or analysed in the current study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Sangru Wu: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Sihang Wang:** Writing – review & editing. **Meina Wu:** Supervision, Investigation, Data curation. **Fang Lin:** Investigation, Data curation. **Xiaolin Ji:** Writing – review & editing, Supervision. **Jinzhu Yan:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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