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Seizures by the clock: Temporal patterns of psychogenic nonepileptic seizures☆

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ABSTRACT

We hypothesized that (1) the occurrence of psychogenic nonepileptic seizures (PNES) is modulated by the interaction between the 24-hour clock and the sleep–wake cycle and (2) the pattern of modulation in PNES differs from epileptic seizures (ES). We sought to test our hypotheses in a cohort of patients diagnosed with PNES or ES in the setting of an epilepsy monitoring unit (EMU). We retrospectively reviewed consecutive video-EEG (VEEG) recordings of patients who underwent monitoring at the EMU of a tertiary hospital. The seizure type (PNES vs ES), onset time, and the state (sleep vs awake) were tabulated. The relationship between the onset time, the state of arousal, and the occurrence of PNES was determined using logistic regression analysis. To determine if the nature of the relationship between the state of arousal and PNES differed according to the onset time, an interaction between the onset time and the state of arousal was also fitted to the model. We studied a total of 754 seizures (ES, 437; PNES, 317) from 135 patients consisting of 71 (52.6%) females and 64 (47.4%) males with the median age of 39 years (range, 18–91). We found a significant association between the state of arousal and PNES with the odds of being PNES four times higher when patients were awake (OR: 4.27, 95% CI: 2.44–7.48; $p < 0.0001$) compared with when they were asleep. The analysis further revealed a significant interaction between the onset time and the state of arousal ($p = 0.004$). The odds of being PNES were significantly higher if the seizure occurred when the patient was awake at night. These patterns possibly indicate the complex interaction between the sleep–wake cycle and the 24-hour time cycle in the generation of PNES.

1. Introduction

Epileptic seizures (ES) are modulated by circadian cycles including the primary circadian clock and the sleep–wake cycle [1]. Temporal patterns of ES have been described by several researchers [2]. The circadian profile varies depending on the seizure type and the location of the seizure focus [2,3]. These studies suggest that the occurrence of ES is not entirely random.

Similar to ES, psychogenic nonepileptic seizures (PNES) manifest with episodic disturbances of motor, sensory, autonomic, or cognitive functions [4]. Psychogenic nonepileptic seizures are conceptualized as involuntary events similar to ES [5]. Hence, it seems logical to think that the occurrence of PNES may also vary during the day. Recognition of temporal patterns of PNES may offer some help in differentiating those from ES. However, to date, there have been no studies conducted to describe the temporal profile of PNES.

We hypothesized that (1) the occurrence of PNES is modulated by the interaction between the 24-hour time clock and the sleep–wake cycle, and (2) the pattern of modulation in PNES differs from ES. We sought to test our hypotheses in a cohort of patients diagnosed with PNES or ES in the setting of an epilepsy monitoring unit (EMU).

2. Methods

2.1. Data acquisition

We retrospectively reviewed all consecutive video-EEG (VEEG) recordings of patients who underwent monitoring at the EMU of Monash Medical Centre, Melbourne, Australia from May 2005 to June 2015. We only included adults (≥18 years) and selected studies which captured PNES or ES. Patients who had a mix of both ES

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Table 1
Epileptic seizure types in the cohort.

Seizure type	Frequency (%)
Focal impaired awareness (complex partial)	285 (65.2)
Generalized tonic	61 (14.0)
Absence	33 (7.6)
Focal aware (simple partial)	17 (3.9)
Focal to bilateral tonic–clonic	15 (3.4)
Generalized myoclonic	14 (3.2)
Generalized tonic–clonic	7 (1.6)
Generalized atonic	5 (1.1)

and PNES during the same VEEG recording were excluded from the current study.

The VEEG data were acquired using the Compumedics digital EEG system (Compumedics Ltd., Melbourne, Australia) with the international 10–20 system of electrode placement. Antiepileptic drug (AED) tapering and sleep deprivation were routine practices in the EMU. We did not use other seizure provocation techniques such as hyperventilation, intermittent photic stimulation, and placebo injections.

We collated clinical and demographic data from medical records. We reviewed all seizures captured on VEEG during the study period. The final diagnosis of PNES or ES was based on the consensus opinion of at least two epileptologists after reviewing clinical information, investigation results, and VEEG findings including semiology. The diagnosis had been established following the VEEG monitoring, in the multidisciplinary meeting, prior to the current study. Hence, seizure mimickers such as sleep disorders and movement disorders were not included in the study cohort. We considered this consensus diagnosis as the "gold standard" for our study. The reader is referred to Seneviratne et al. [6] for a more detailed account.

For the current study, two investigators, an epileptologist (US) and an EEG technologist (EM), studied each seizure video carefully, in synchrony with the EEG, to record the time of ictal onset. We also tabulated the state of arousal at the seizure onset. The state of arousal (awake vs sleep) was determined according to the guidelines on visual scoring published by the American Academy of Sleep Medicine [7]. If the seizure onset occurred during sleep or within 20 s of an arousal or awakening, it was considered to be a sleep- or arousal-related seizure.

2.2. Statistical analyses

All data were analyzed using Stata software version 14 (StataCorp, Texas, USA). To compare the temporal distribution of epileptic and nonepileptic seizures, onset time over the 24-hour day was divided into four bins in keeping with previous research [8]. The time bins were 05:00–11:00 h (I), 11:00–17:00 h (II), 17:00–23:00 h (III), and 23:00–05:00 h (IV), consecutively. The proportion of seizures in each of the four time bins was estimated and reported with 95% confidence intervals. The relationship between onset time (I, II, III, and IV), the state of arousal (awake vs sleep), and occurrence of PNES was determined using logistic regression analysis. To account for multiple seizures per patient, robust standard errors were estimated using the 'cluster' option in Stata. The cluster option was used to obtain standard errors based on the sandwich estimator that take clustering into account, thus allowing for differences in the variances due to intrapatient correlation. To further examine if the nature of the relationship between the state of arousal and PNES differs according to onset time bins, an interaction between the onset time and the state of arousal was also fitted to the model with results reported as odds ratios (OR) and 95% confidence intervals (95% CI). All calculated p values were two-tailed, and $p < 0.05$ indicated statistical significance.

The study protocol was approved by the Human Research Ethics Committees of Monash Health.

Table 2
Temporal distribution of ES and PNES over the 24-hour day.

Onset time (bin)	Epileptic (n = 437)	PNES (n = 317)	Difference (95% confidence interval)	p value
05:00 to 11:00 h (I)	102 (23.3%)	66 (20.8%)	2.5% (−9.8 to 14.8)	0.69
11:00 to 17:00 h (II)	106 (24.3%)	88 (27.8%)	3.5% (−6.3 to 13.3)	0.48
17:00 to 23:00 h (III)	117 (26.8%)	93 (29.3%)	2.5% (−6.7 to 11.8)	0.58
23:00 to 5:00 h (IV)	112 (25.6%)	70 (22.1%)	3.5% (−9.1 to 16.2)	0.58

Table 3
Distribution of ES and PNES according to the state of arousal.

Type of seizure	Sleep status		Difference (95% confidence interval)	p value
	Sleep	Awake		
ES	181 (41.4%)	256 (58.6%)	17.2% (−2.2 to 36.5)	0.08
PNES	45 (14.2%)	272 (85.8%)	71.6% (61.9 to 81.3)	<0.0001

3. Results

We studied a total of 754 seizures (ES, 437; PNES, 317) from 135 patients consisting of 71 (52.6%) females and 64 (47.4%) males with the median age of 39 years (range, 18–91). A higher proportion of females were seen in the group with PNES compared with the group with ES (71% vs 37%). Median ages of ES and PNES cohorts were comparable (39 & 37.5 years, respectively). Epileptic seizures were captured from 73 (54.1%) patients, whereas 62 (45.9%) had only PNES. In the group with "ES alone", 62 (84.9%) and 11 (15.1%) had focal and generalized epilepsy syndromes, respectively. Different ES types in the cohort are summarized in Table 1. The mean duration of VEEG monitoring was 4.5 ± 1.5 days.

Table 2 shows the temporal distribution of ES and PNES in six-hourly time bins over the 24-hour day. There was no significant difference in the proportion of ES and PNES across the four time bins. However, there was a significant association between the state of arousal and PNES with the odds of being PNES 4 times higher when patients were awake (OR: 4.27, 95% CI: 2.44–7.48; $p < 0.0001$) compared with when patients were asleep. Similarly, if a seizure occurred in sleep, the odds were 77% lower for it to be PNES (OR: 0.23, 95% CI: 0.13–0.41; $p < 0.0001$) (Table 3). Figs. 1 and 2 further highlights the temporal distribution of seizures throughout the day and in relation to the state of arousal (awake vs sleep).

Forty-five sleep- or arousal-related PNES were captured from 12 patients (30 PNES in sleep and 15 within 20 s of arousal/awakening). Three patients were diagnosed with having intellectual disabilities while five had reported having seizures in sleep. All patients with sleep- or arousal-related PNES had seizures in wakefulness as well as during the VEEG monitoring. They had similar seizure semiologies in sleep and wakefulness.

The analysis further revealed a significant interaction between the onset time and the state of arousal ($p = 0.004$) suggesting that the nature of the relationship between awake vs sleep, and PNES differed according to the onset time as shown in Table 4. Although there was no association between the state of arousal and PNES in the early hours of the day, significant associations were found for evening and night times. The odds of being PNES were about 6 times higher if the seizure occurred when patient was awake in the evening (time bin III). This relationship was stronger with an odds ratio of 14.34 for patients who had seizures when they were awake compared with those who were asleep from 23:00 to 05:00 h.

Some ES and PNES occurred late night in wakefulness as a result of sleep deprivation. Table 5 provides the breakdown of clinical events at night during sleep and wakefulness.

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