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Are seizures in the setting of sleep deprivation provoked?☆

Nicholas Lawn *[,1], Sam Lieblich [1], Judy Lee [1], John Dunne [1]

Department of Neurology, Royal Perth Hospital, Perth, Western Australia, Australia

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ABSTRACT

It is generally accepted that sleep deprivation contributes to seizures. However, it is unclear whether a seizure occurring in the setting of sleep deprivation should be considered as provoked or not and whether this is influenced by seizure type and etiology. This information may have an important impact on epilepsy diagnosis and management. We prospectively analyzed the influence of sleep deprivation on the risk of seizure recurrence in patients with first-ever unprovoked seizures and compared the findings with patients with first-ever provoked seizures. Of 1026 patients with first-ever unprovoked seizures, 204 (20%) were associated with sleep deprivation. While the overall likelihood of seizure recurrence was slightly lower in sleep-deprived patients with first-ever seizures (log-rank $p = 0.03$), sleep deprivation was not an independent predictor of seizure recurrence on multivariate analysis. Seizure recurrence following a first-ever unprovoked seizure associated with sleep deprivation was far more likely than for 174 patients with a provoked first-ever seizure (log-rank $p < 0.0001$). Our findings support the International League Against Epilepsy recommendation that seizures occurring in the setting of sleep deprivation should not be regarded as provoked.

1. Introduction

A common clinical presentation, often in a young adult, is with a first-ever seizure in the setting of significant sleep deprivation. While it is generally accepted that sleep deprivation contributes to seizures, it is unclear whether seizures occurring in this situation should be regarded as provoked. The International League Against Epilepsy (ILAE) guidelines for epidemiologic studies on epilepsy do not define seizures associated with sleep deprivation as provoked [1], but the rationale for this has not been systematically studied. This information may have an important impact on the diagnosis and management of epilepsy. To clarify this issue, we analyzed the likelihood of seizure recurrence in patients with first-ever unprovoked seizures occurring with and without sleep deprivation. The findings were compared with those of patients with first-ever seizures related to a clearly defined proximate cause.

2. Methods

The Western Australian first-seizure database, established in 2000, is an ongoing prospective study of adults with first-ever seizures seen by a hospital-based epilepsy service aiming to identify outcomes and risk factors for seizure recurrence. The methodology has previously been described [2,3]. All patients underwent a standardized assessment with specific questions on potential seizure precipitants including the presence of sleep deprivation prior to the seizures. Sleep deprivation was defined as an exceptional lack of sleep for that patient, requiring 50% or less of their usual sleep, typically less than 4 h, over the 24 h prior to the seizures [4,5]. Seizure type, etiology, and electroclinical syndrome (focal-in-onset, generalized-in-onset, or unclassified) were categorized for the presenting seizures according to published guidelines [1]. Unprovoked seizures were defined as "remote symptomatic" if there was a history of or neuroimaging evidence for a prior CNS insult (including brain tumors) and "idiopathic" if there was no obvious cause (encompassing genetic epilepsy syndromes and "cryptogenic" seizures).

2.1. Follow-up

Patients were assessed in the clinic three to nine months after the index seizure and, if there had been no further seizures, were thereafter contacted by phone every one to two years until seizure recurrence occurred or death. For those who were not contactable by phone, the integrated hospital computer system was checked for attendance at other major hospitals in Western Australia, and if so, the related medical records were obtained. A second seizure occurring during follow-up, provoked or unprovoked, was considered a recurrence. The circumstances of any seizure recurrence were also documented including whether sleep deprivation was present. Patients who had a second seizure after being referred but prior to being seen at the clinic were included, with

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* Corresponding author at: Department of Neurology, Royal Perth Hospital, GPO Box X2213, Perth, Western Australia 6847, Australia. Tel.: +61 8 9224 2593; fax: +61 8 9224 7020.
E-mail address: nicholas.lawn@health.wa.gov.au (N. Lawn).

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the initial seizure being analyzed as the first seizure and the second being defined as a recurrence.

2.2. Study aims and statistical analysis

The hypothesis was that sleep deprivation was not an independent predictor of recurrence after a first-ever unprovoked seizure and, unlike first seizures with a clearly defined proximate cause, was not associated with a lower risk of recurrence. We compared the clinical features and prognosis (occurrence of a second seizure) in patients with first-ever unprovoked seizures with sleep deprivation with those without sleep deprivation and according to seizure etiology. Comparisons between groups were conducted using *t* tests and analysis of variance for normally distributed data and the Mann–Whitney or the Kruskal–Wallis test for non-normal data. The chi-squared and Fisher exact tests were used to analyze categorical data. Holm's method was used to correct for multiple comparisons. Patients with missing data were excluded from univariate analyses. A comparison was also made in patients satisfying the ILAE criteria for a provoked first-ever seizure [1], excluding those with a CNS lesion known to predispose to further seizures and those patients who were also sleep-deprived. Seizure recurrence was analyzed using Kaplan–Meier curves and log-rank statistics. Sleep deprivation and other variables potentially predictive of seizure recurrence identified in prior first-seizure studies were examined using Cox proportional hazards models [2,3,6]. Variables significant at the 10% level in preliminary univariate analyses were included in the multivariate models. Hazard ratio (HR), odds ratio (OR), and 95% confidence interval (CIs) for multivariate analyses were calculated from the final models. Results were considered statistically significant at the 5% level.

The study was approved by the Royal Perth Hospital Ethics Committee.

3. Results

3.1. Unprovoked seizures

One thousand twenty-six of 1032 patients with first-ever unprovoked seizures were studied; six patients were excluded because of an absence of information on sleep deprivation status. EEG and neuroimaging (CT, MRI, or both) were performed in 99% and 98% of patients, respectively, and, equally, in sleep-deprived and nonsleep-deprived patients. The clinical and investigation findings are summarized in Table 1. Stepwise logistic regression showed that sleep-deprived patients with unprovoked seizures were both younger (OR = 0.97, 95% CI = 0.96–0.98, $p < 0.001$) and more likely have generalized epileptiform abnormalities (OR = 2.1, 95% CI = 1.2–3.4, $p = 0.005$).

Overall, a first seizure in association with sleep deprivation had a slightly lower likelihood of seizure recurrence when compared with nonsleep-deprived patients (log-rank $p = 0.03$; Fig. 1); but this difference was not evident when comparing the annual rate of seizure recurrence (Table 2). Patients with generalized-onset first-ever seizures were more likely to be sleep-deprived (21%) compared with patients with focal-onset seizures (6%) ($p = 0.002$), but recurrence rates were similar regardless of seizure type (Fig. 2). Cox proportional hazards modeling found that sleep deprivation was not predictive of seizure recurrence. The independent predictors of seizure recurrence were remote symptomatic etiology (HR = 1.36, 95% CI = 1.15–1.62, $p < 0.001$), epileptiform abnormalities on EEG (HR = 1.40, 95% CI = 1.15–1.71, $p = 0.001$), seizures from sleep (HR = 1.27, 95% CI = 1.05–1.52, $p = 0.01$), and a focal-onset seizure (HR = 1.65, 95% CI = 1.21–2.27, $p = 0.001$). Treatment did not alter seizure recurrence rate irrespective of etiological subgroup or seizure type. For patients with unprovoked first-ever seizures in whom no cause could be identified on imaging and EEG was normal (n = 565, 20% were sleep-deprived), the presence of sleep deprivation did not alter the risk of recurrence. Data on the presence of sleep deprivation with the second seizure were available in 96% of the patients who had an unprovoked recurrence. If the first unprovoked seizure was sleep deprived, a second unprovoked seizure was also sleep deprived in 29% compared with 5% of recurrences when sleep deprivation was not present with the first seizure ($p < 0.0001$).

3.2. Provoked first seizures

One hundred seventy-four patients with first seizures in association with an accepted provoking factor by the ILAE criteria were identified, excluding 100 patients with a CNS lesion and 122 with sleep deprivation (Table 1). The causes were as follows: alcohol-related — 34 (19%), drug withdrawal or overdose — 28 (16%), metabolic — 17 (10%), prescribed drug — 76 (44%), illicit drug — 15 (9%), and other — 4 (2%). The

Table 1
Clinical and EEG findings in sleep-deprived and nonsleep-deprived patients with first-ever unprovoked seizures.

	Unprovoked N = 1026		p value[a]	Provoked N = 174
	Sleep-deprived (n = 204)	Nonsleep-deprived (n = 822)		
Gender male n (%)	122 (60)	527 (64)	ns	90 (52)
Median age, years (range)	33 (14–87)	43 (14–91)	<**0.0001**	34 (15–85)
First-degree relative with epilepsy n (%)	20 (10)	85 (11)	ns	14 (8)
Seizure type				
Tonic–clonic n (%)	200 (98)	755 (92)		175 (100)
Other n (%)	4 (2)	67 (8)	**0.001**	0
Electroclinical diagnosis				
Focal n (%)	73 (36)	431 (52)		15 (9)
Generalized n (%)	37 (18)	54 (7)		13 (7)
Unclassified n (%)	94 (46)	337 (41)	<**0.0001**	146 (84)
Seizure from sleep n (%)	38 (19)	200 (24)	ns	10 (6)
Cluster n (%)	24 (12)	156 (19)	0.02	38 (22)
Status n (%)	4 (2)	15 (2)	ns	4 (2)
Epileptiform n (%)	49 (24)	124 (16)	**0.007**	14 (8)
Focal n (%)	17 (8)	77 (10)	ns	2 (1)
Generalized n (%)	32 (16)	47 (6)	<**0.0001**	12 (7)
Epileptogenic lesion on CT or MRI n (%)	40 (20)	254 (31)	**0.001**	0
Treated after first seizure n (%)	27 (13)	238 (29)	<**0.0001**	21 (12)
Mean duration of follow-up, days (range)	1635 (7–4389)	1458 (4–4341)	0.03	1372 (30–4202)

Those remaining significant after the correction for multiple comparisons are indicated in bold.
[a] p values are for univariate, comparisons between unprovoked sleep-deprived and nonsleep-deprived patients.