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Can epilepsy affect normal EEG variants? A comparative study between subjects with and without epilepsy

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ABSTRACT

Objectives: To compare the prevalence of benign EEG variants (BEVs) between epileptic and non-epileptic subjects.
Methods: A prospective, observational EEG study of 1,163 consecutive patients, using the 10−20 international system with systematically two additional anterior/inferior temporal electrodes. The video-EEG monitoring duration was between 24 h and eight days.
Results: We identified 917 (78.9%) epileptic patients (mean age: 33.42 ± 15.5 years; females: 53.4%) and 246 (21.2%) non-epileptic patients (mean age: 35.6 ± 18.75 years; females: 54.9%). Despite a shorter mean duration of the EEG recordings, the prevalence of BEVs was higher in non-epileptic vs. epileptic patients (73.2% vs. 57.8%, $p = 0.000011$). This statistical difference was confirmed for lambda waves (23.6% in the non-epilepsy group vs. 14.8% in the epilepsy group, $p = 0.001$), POSTs (50.8% vs. 32.5%, $p < 0.000001$), wicket spikes (20.3% vs. 13.6%, $p = 0.009$) in particular in NREM and REM sleep, and 14- and 6-Hz positive bursts (13% vs. 7.1% $p = 0.003$). Mu rhythm was observed at the same frequency in both groups (21.1% in the non-epilepsy group vs. 22.7% in the epilepsy group). There was no difference between the two groups for rarer rhythms, such as rhythmic mid-temporal theta burst of drowsiness, small sharp spikes, and midline theta rhythm.
Conclusions: There was no increase in any of the BEVs in the epilepsy group. On the contrary, BEVs were more frequent and diversified in the non-epilepsy group. Epilepsy may negatively affect the occurrence of the most common BEVs, with the exception of the mu rhythm, which is present in about one-fifth of the population with or without epilepsy.

Introduction

Benign EEG variants (BEVs) are recognizable EEG patterns that pose a challenge in their interpretation due to their epileptiform or rhythmic nature. They are electroencephalographic activities of varying prevalence, that can be classified based on one of three specific characteristics [9]. The sharp variants include wicket spikes (WS), small sharp spikes (SSS), 14- and 6-Hz positive bursts, and 6-Hz spike and wave bursts. The rhythmic variants include mu rhythm, midline theta rhythm, rhythmic mid-temporal theta burst of drowsiness (RMTD), and subclinical rhythmic electrographic discharge of adults (SREDA). Posterior variants include lambda waves and positive occipital sharp transients of sleep (POSTs). When first described, some BEVs were associated with psychiatric disorders, neurologic symptoms, or epilepsy [15,1]. After further studies, most authors now consider their occurrence common in patients without epilepsy. However, there remains some uncertainty, notably for SSS, 14- and 6-Hz positive bursts, and 6-Hz spike and wave bursts [15].

That being said, epilepsy may influence physiological EEG patterns, such as sleep spindles. In focal epilepsies, EEG asymmetry can be seen, with spindles better organized in the hemisphere contralateral to the epileptic focus [2,21]. In this study, we prospectively evaluated BEVs in 917 epileptic and 246 non-epileptic patients and compared their prevalence. All patients in this study underwent continuous video-EEG monitoring for at least 24 h to investigate the distribution of each type of BEV in both groups according to the sleep-wake cycle.

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Methods

Study design

This is an observational, prospective study conducted among all patients who underwent prolonged video-EEG monitoring (from one to eight days) in the medical-surgical epilepsy unit of the University Hospital of Montpellier (France) from the 1st January 2009 to the 30th April 2018. All patients were prospectively included in an anonymous database. Written informed consent was obtained from all patients participating in this study. EEG data were recorded using 21 scalp electrodes (10−20 international system), with systematically two additional anterior-temporal electrodes on each side, and depending on clinical indications, other electrodes were added. The video-EEG monitoring duration was between 24 h and eight days, depending on the context. The detailed EEG methodology and EEG analysis have been published elsewhere [13].

Study population

Based on diagnosis, the study population was divided into two groups (epileptic versus non-epileptic patients). Epilepsy was classified using the International League against Epilepsy classification [20] by type of epilepsy and by etiology.

EEG analysis and clinical data

EEGs and clinical data were analyzed by two board-certified neurophysiologists/epileptologists (P.G. or A.C), and the database included the results only after joint validation.

Statistical analysis

Characteristics of the study population were expressed as means and standard deviations (SD), with frequencies and proportions for categorical variables, and median and range (or mean and SD) for continuous variables. All analyses were two-tailed, with a p-value of <0.05 considered statistically significant. Statistical analysis was performed using SAS® Enterprise Guide software (SAS Institute, Cary, NC, USA) version 7.12.

Results

The study population included 1163 patients with a mean age of 33.9 ± 16.3 years (range 1−84). There were 625 females (53.7%) and 538 males (46.3%) (Table 1). The detailed results of this cohort and the BEVs in the wake/sleep stages have been previously published [13]. Of these, 710 patients had at least one BEV (sex ratio F/M 1.43). Out of 1163 subjects, there were 917 patients (78.9%) with a diagnosis of epilepsy (mean age: 33.42 ± 15.5 years; females: 53.4%) and 246 (21.2%) non-epileptic patients (mean age: 35.6 ± 18.7 years; females: 54.9%). The epileptic syndromes, etiologies of the epilepsies, and the final diagnosis of non-epileptic patients are presented in Table 1.

Despite a shorter mean duration of the EEG recordings (37.66 ± 14.7 h versus 46.98 ± 25.1, $p < 0.001$), the prevalence of BEVs was higher in non-epileptic patients than epileptic patients (73.2% versus 57.8%, $p = 0.000011$) (Table 2). In particular, this statistical difference was confirmed for lambda waves (23.6% in non-epileptic patients versus 14.8% in epileptic patients, $p = 0.001$), POSTs (50.8% versus 32.5%; $p < 0.000001$), WS (20.3% versus 13.6%; $p = 0.009$), and 14- and 6-Hz positive bursts (13% versus 7.1%; $p = 0.003$). For WS, a statistical difference was observed only for transients recorded during NREM and REM sleep, but not during wakefulness. Mu rhythm was observed at the same frequency in both groups (21.1% in the non-epilepsy group versus 22.7% in the epilepsy group). RMTD, SSS, midline theta rhythm were seen at low frequency, and there was no significant difference between the two groups (Table 2). In this cohort of 1163, we only identified one

Table 1
Type of epilepsy according to the International League Against Epilepsy classification (2017).

Variable		Frequency	Percentage
Sex	Male	538/1163	53.7%
	Female	625/1163	46.3%
Non-epilepsy group		246/1163	21.2%
Type of diagnosis in non-epileptic subjects	Single seizure without EEG abnormalities	23/246	9.4%
	Psychiatric disease	85/246	34.6%
	Cerebrovascular disease	2/246	0.8%
	Cardiologic disease	41/246	16.7%
	Metabolic disease	2/246	0.8%
	Movements disorders	15/246	6.1%
	Headache	18/246	7.3%
	Sleep disorders	16/246	6.5%
	Others	44/246	17.9%
Epilepsy group		917/1163	78.9%
Type of epilepsy	Generalized epilepsy	272/917	29.7%
	Focal epilepsy	622/917	67.8%
	Undetermined epilepsy	20/917	2.2%
	Generalized and focal epilepsy	3/917	0.3%
Etiology of epilepsy	Unknown	319/917	34.8%
	Genetic	261/917	28.5%
	Structural	318/917	34.7%
	Infectious	16/917	1.7%
	Metabolic	2/917	0.2%
	Immune	1/917	0.1%

Table 2
Comparison between epilepsy and non-epilepsy groups.

	Epilepsy group (N = 917)	Non-epilepsy group (N = 246)	P
Females	490 (53.4%)	135 (54.9%)	0.687
Males	427 (46.6%)	111 (45.1%)	
Age (mean ± DS)	33.42 ± 15.5	35.6 ± 18.7	0.407
Mean duration of EEG monitoring (hours)	46.98 ± 25.1	37.66 ± 14.7	**<0.001**
BEVs	530 (57.8%)	180 (73.2%)	**0.000011**
Mu rhythm	208 (22.7%)	52 (21.1%)	0.606
• in wakefulness	174 (19%)	44 (18%)	0.698
• in NREM sleep	12 (1.3%)	5 (2%)	0.377
• in REM sleep	72 (7.9%)	17 (6.9%)	0.622
Lambda waves	136 (14.8%)	58 (23.6%)	**0.001**
POSTs	298 (32.5%)	125 (50.8%)	**<0.000001**
Midline theta rhythm	22 (2.4%)	2 (0.8%)	0.120
Wicket spikes	125 (13.6%)	50 (20.3%)	**0.009**
• in wakefulness	25 (2.7%)	9 (3.7%)	0.441
• in NREM sleep	119 (13%)	45 (18.3%)	**0.033**
• in REM sleep	23 (2.5%)	15 (6.1%)	**0.005**
RMTD	19 (2.1%)	6 (2.4%)	0.724
• in wakefulness	8 (0.9%)	3 (1.2%)	0.709
• in NREM sleep	10 (1.1%)	5 (2%)	0.334
• in REM sleep	11 (1.2%)	2 (0.8%)	1.0
14- and 6-Hz positive bursts	65 (7.1%)	32 (13%)	**0.003**
• in NREM sleep	29 (3.2%)	23 (9.4%)	**0.000031**
• in REM sleep	52 (5.7%)	23 (9.4%)	**0.037**
SSS	33 (3.6%)	5 (2%)	0.221
Six-Hz Spike and Wave bursts	1 (0.1%)	0 (0%)	1.00
Number of rhythms			
• 1	271 (29.6%)	81 (32.9%)	**0.000096**
• 2	166 (18.1%)	58 (23.6%)	
• 3	71 (7.7%)	34 (13.8%)	
• ≥4	22 (2.4%)	7 (2.9%)	

Bold values indicate significant results.

patient with 6-Hz spike and wave bursts and no patient with SREDA [13], which is too rare to draw a conclusion.

Regarding the number of BEVs, 32.9% of non-epileptic patients versus 29.6% of epileptic patients had just one BEV, 23.6% versus 18.1% had two BEVs, 13.8% versus 7.7% had three BEVs and 2.9% versus 2.4% had more than four BEVs ($p = 0.000096$) (Table 2).

Discussion

This study reports the prevalence of BEVs in patients with and without epilepsy, utilizing recordings from patients who underwent prolonged video EEG monitoring for at least 24 h to assess the prevalence of each BEV along the sleep-wake cycle. Many of the BEVs described in this study exhibit an age-dependent pattern, especially POSTs [17] and 14- and 6-Hz positive bursts [25], occurring more frequently in young people and becoming less frequent with advancing age. However, there was no statistical difference between the groups based on gender and age at the time of evaluation (Table 2).

Taken individually, there was no increase in any particular type of BEV in the epilepsy group. Earlier studies have suggested a possible link between some EEG variants and epilepsy. Koshino and Niedermeyer (1975) reported a prevalence of SSS of 1.36%. Two-thirds of those patients had a history of epileptic seizures [12]. From an EEG laboratory with many referrals with epilepsy, there was a 48% incidence of clinical seizures in patients with SSS, whereas the number was 15% in patients with a normal EEG [7]. In a study comparing epileptic patients and non-epileptic individuals, the occurrence of SSS was higher in the first group (8.6% versus 2.5%) [18]. Subsequent studies do not demonstrate a correlation between SSS and epilepsy [15,1,14]. However, a recent study with intracranial electrodes demonstrated that some hippocampal spikes can manifest as SSS on a scalp EEG [8]. In our cohort, during nocturnal sleep, we found a prevalence of SSS of about 3% [13], which was slightly higher in the epilepsy group (3.6% versus 2%) but without any statistical difference between the two groups, in favor of the absence of any link.

It has also been reported that epilepsy is more frequent in patients with 14- and 6-Hz positive bursts [6,27]. These initial reports did not provide sufficient documentation of epilepsy, lacked appropriate control groups, and did not fully acknowledge the significant impact of age on the manifestation of this pattern [11]. Indeed, these bursts are mainly seen in younger people, as we previously reported (prevalence of 62% in patients aged 15−25 years) [25]. In this cohort of 1163 patients, the prevalence of 14- and 6-Hz positive bursts of more than 8% was significantly higher than in previous reports (0.5% - 5.68%) [16,19]. The age distribution was similar in epilepsy and non-epilepsy groups. There was a significantly higher prevalence of 14-and 6-Hz in the non-epilepsy group (13% versus 7%, $p = 0.003$), confirming that this pattern has no relationship to epilepsy.

Six-Hz spike-and-wave bursts, also known as phantom spike-and-wave bursts, exhibit patterns that can be ambiguous. This pattern may be associated with seizures [24]. Two different types are proposed by considering gender, topography, and the state of vigilance. The first type, known as WHAMs (wake high amplitude anterior predominance in males), is more commonly associated with epilepsy. The second type, FOLDs (female occipital predominant low amplitude and drowsiness), would correspond to a benign variant [5]. Our prevalence rate among the 1163 patients is less than 0.1% (1 case in the epilepsy group) and is significantly lower compared to previous studies. This reflects the suggestive aspect of this pattern, which perhaps should not be classified among BEVs. The interpretation relies on the clinical context. In non-epileptic patients, they are classified as BEVs, whereas in genetic (idiopathic) generalized epileptic patients, they are often seen as a characteristic of the epileptic syndrome.

This study provides evidence that there is no link between epilepsy and each of the individual BEVs. On the contrary, despite the shorter mean duration of the EEG recordings in the non-epilepsy group, we found that BEVs were more frequent and diversified in this group, and patients tended to have multiple types of BEVs. In this cohort of 1163 patients, the mu rhythm was observed in more than 20% of the population, with no difference between the two groups. POSTs, WS, lambda waves, and 14- and 6-Hz positive bursts were found to be significantly less frequent in epileptic patients. The sample size for rhythms observed at a frequency of less than 3% is too small to allow us to draw a conclusion about the relative prevalence between groups.

Although the impact of seizure frequency and the type and number of antiseizure drugs at the time of evaluation were not specifically investigated, this study suggests that epilepsy itself may negatively interfere with the most frequent BEVs. For physiological EEG patterns, the influence of epilepsy on the microstructure as well as on the macrostructure of sleep is well known both in focal and generalized epilepsies [2−4,10]. In temporal lobe epilepsy, it has been suggested that surgery, by greatly decreasing seizure frequency and the use of antiseizure drugs, may contribute to improving sleep architecture [22]. In patients with focal epilepsy, the presence of an epileptic focus can result in a decrease in both global and local spindle rates [21]. More specifically, the region that contains the epileptic focus shows reduced spindle rates [21,2]. In focal epilepsies, a reduction in K complex density has been observed [4]. However, in nocturnal frontal lobe epilepsy, which is an infrequent epileptic syndrome [26], Si et al. (2010) reported that the activity of K complexes is increased, reflecting for the authors, an increased arousal reaction [23].

In conclusion, this study provides evidence of the absence of a link between specific types of EEG variants and epilepsy. As the most frequent BEVs, such as POSTs, WS, lambda waves, and 14- and 6-Hz positive bursts are less frequent in epileptic patients, epilepsy may negatively affect the occurrence of these EEG variants, with the exception of the mu rhythm, which is present in about one-fifth of the population with or without epilepsy.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Nilo, Dr Macorig, Dr. Tang, Dr Gigli report no conflicts of interest relevant to this article. Dr. Gélisse and Dr Crespel received honoraria from John Libbey Eurotext.

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