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24-hour rhythmicity of seizures in refractory focal epilepsy

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ABSTRACT

The occurrence of seizures in specific types of epilepsies can follow a 24-hour nonuniform or nonrandom pattern. We described the 24-hour pattern of clinical seizures in patients with focal refractory epilepsy who underwent video-electroencephalography monitoring. Only patients who were candidates for epilepsy surgery with an unequivocal seizure focus were included in the study. A total of 544 seizures from 123 consecutive patients were analyzed. Specific time of seizures were distributed along 3- or 4-hour time blocks or bins throughout the 24-hour period. The mean age of the subjects was 37.7 years, with standard deviation of 11.5 years, median of 37. The majority were females (70/56%). The majority of patients had a seizure focus located in the mesial temporal lobe (102/83%) and in the neocortical temporal lobe (13/11%). The remaining patients had a seizure focus located in the extratemporal lobe (8/6%). The most common etiology was mesial temporal sclerosis (86/69.9%). Nonuniform seizure distribution was observed in seizures arising from the temporal lobe (mesial temporal lobe and neocortical temporal lobe), with two peaks found in both 3- and 4-hour bins: 10:00–13:00/16:00–19:00 and 08:00–12:00/16:00–20:00 respectively ($p = 0.004$). No specific 24-hour pattern was identified in seizures from extratemporal location. The 24-hour rhythmicity of seizure distribution is recognized in certain types of epilepsy, but studies on the topic are scarce. Their replication and validation is therefore needed. Our study confirms the bimodal pattern of temporal lobe epilepsy independently of the nature of the lesion. However, peak times differ between different studies, suggesting that the ambient, rhythmic exogenous factors or environmental/social zeitgebers, may modulate the 24-hour rhythmicity of seizures. Characterization of these 24-hour patterns of seizure occurrence can influence diagnosis and treatment in selected types of epilepsy, such as the case of temporal lobe epilepsy, the most common drug-resistant epilepsy.

1. Introduction

The occurrence of seizures in specific types of epilepsies can follow specific 24-hour patterns with nonrandom distribution [1–10]. Circadian or sleep–wake related variations of different hormones, neuromediators, and or body temperature are among the potential factors that could contribute to fluctuations of neuronal excitability and propensity for seizure occurrence [2,4,7,11,12]. Even with the advances in the management of epilepsy, seizures of up to 30% of patients with epilepsy remain refractory to treatment [13]. The knowledge about the occurrence of seizures in relation to the 24-hour period offers a potential window of opportunity for therapeutic and diagnostic optimization [14]. Despite the relevance of studying the 24-hour pattern of seizure occurrence, studies on the topic are scarce. Therefore, we sought to characterize the 24-hour occurrence of seizures in adult patients with focal refractory epilepsy included in our epilepsy surgery program.

2. Materials and methods

We reviewed the Sleep and Epilepsy Laboratory database from a tertiary University Hospital (the Neurology Department of the Hospital de Santa Maria (HSM) in Lisbon) to identify patients admitted to the epilepsy monitoring unit for preoperative evaluation from 2004 to 2012. Patients older than 18 years with refractory focal epilepsy were consecutively included if concordance between video-electroencephalography (video-EEG), clinical features, and imaging findings were sufficient to indicate neurosurgical treatment. Electroencephalogram (EEG) data were recorded using standard 10–20 system electrode placements plus inferior temporal electrodes from Nihon Kohden Neurofax EEG-1200 EEG System©. All patients underwent continuous video-EEG monitoring for a period that ranged from 24 h to 10 days (mean: 5.5, median: 6 days). Parents and/or their relatives were encouraged to press the seizure alarm when

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suspicious events occurred. Video recordings were performed by digital closed-circuit video cameras and were continuously monitored during the total time of monitoring. Video-EEG data were firstly analyzed by neurophysiology technicians and then reanalyzed by at least one experienced clinical epileptologist and neurophysiologist. Seizures were defined by the occurrence of any transient neurological or dysautonomic signs and/or symptoms associated with sequential EEG rhythmic or periodic (≥1 Hz) waves with unequivocal evolution in frequency (at least 1/s) or location (at least 2 electrodes).

The analysis included demographics (age at the time of monitoring, gender, duration of epilepsy) and specific seizure descriptors—seizure focus, etiology, the International League Against Epilepsy (ILAE) seizure type, and the time of onset during the 24-hour cycle. Each 24-hour period (07 AM to 07 PM or 8 AM to 8 PM) was divided in time blocks or bins and analyzed using the absolute number of seizures from all individuals that occurred in each bin. Although only the 3-hour bin analysis is included in the manuscript, the 4-hour bin analysis was also performed to facilitate comparison with previous and future studies (supplementary file). As used previously, we limited analysis to the first 8 seizures for each patient to reduce bias that could be introduced by patients with a large number of seizures [2,4,8]. Patients with more than 15 seizures in any 6-hour consecutive period were excluded to minimize the risk of erroneous peaks in seizure occurrence [5]. We also excluded patients whose seizure focus was not defined at the time of analysis, patients with severe psychiatric disorders, pregnant patients, patients with status epilepticus, or patients with any infectious or metabolic medical complications during the monitoring. Only seizures with electrographic confirmation were included in the analysis. This study was approved by the Institutional Review Board of the Centro Hospitalar Lisboa Norte, Hospital de Santa Maria, Lisbon.

2.1. Data analysis

The data were entered into an Excel spreadsheet and analyzed using Spearman's rank correlation coefficient—SPSS 21.0© (SPSS Inc., Chicago, IL). An exploratory analysis including a descriptive and univariate analysis of demographic variables (age, gender, education), clinical features (type of epilepsy—simple focal, complex, with secondary generalization, epilepsy duration), location of the epileptogenic zone (neocortical temporal, mesial temporal, extratemporal), and the nature of the epileptogenic lesion (sclerosis mesial, dysplasia, malformations of cortical development, reactive gliosis, vascular lesions, and abnormal neuronal migration) was performed. To test the bivariate association between the distribution of seizures by each bin (the main dependent variable) and the remaining variables, we used the chi-square test of Pearson ($\chi 2$) for categorical variables and Mann–Whitney (U) or Kruskal–Wallis ($\chi 2$) for non-normally distributed continuous variables. Results were considered statistically significant when the p-value was lower than 0.05.

3. Results

Of the 192 adult patients with focal epilepsy included in the institutional epilepsy surgery program database during this period, 123 met the inclusion criteria. Sixty-nine patients were excluded because of incomplete data/discordant findings between the clinical, EEG and imaging findings (30), generalized epilepsy (26), absence of seizures (11), and complications (2) during monitoring. The mean age was 37.7 years (SD = 11.5), and the median was 37. Most patients were female (70/56.9%). The mean duration of epilepsy before monitoring was 22.7 years (1–54 years). Seizures were complex focal in 69 (56%), simple focal in 7 (5.7%), and focal with generalization in 47 (38.3%). The majority of identified structural lesions were mesial temporal (102/83%) and temporal neocortical (13/11%). The remaining lesions (8/6%) grouped as extratemporal were located in the parietal (4) and frontal (4) lobes. Regarding the etiology of epilepsy, mesial temporal sclerosis (86/69.9%) and tumors (18/14.6%) were the most common type of epileptogenic lesion. Cortical developmental malformations (7/5.7%), reactive gliosis (5/4%), vascular injuries (4/3.2), and abnormal neuronal migration (3/2.6%) were also present. Eighty-four (68.3%) patients underwent surgical resection. The mean follow-up was 57.4 weeks (7–95 weeks). At the last follow-up, 74 (88%) were free of seizures (Engel I), and 6 (7.1%) were almost seizure-free (Engel II). Seizure reduction for prolonged periods occurred in 4 (4.9%) patients (Engel III). A total of 544 seizures were included in the analysis with a mean of 4.4 seizures per patient. Regarding the contribution of each epileptogenic origin, seizures were distributed as follows: mesial temporal lobe (463/85.1%), neocortical temporal lobe (52/9.3%), and extratemporal origin (30/5.6%).

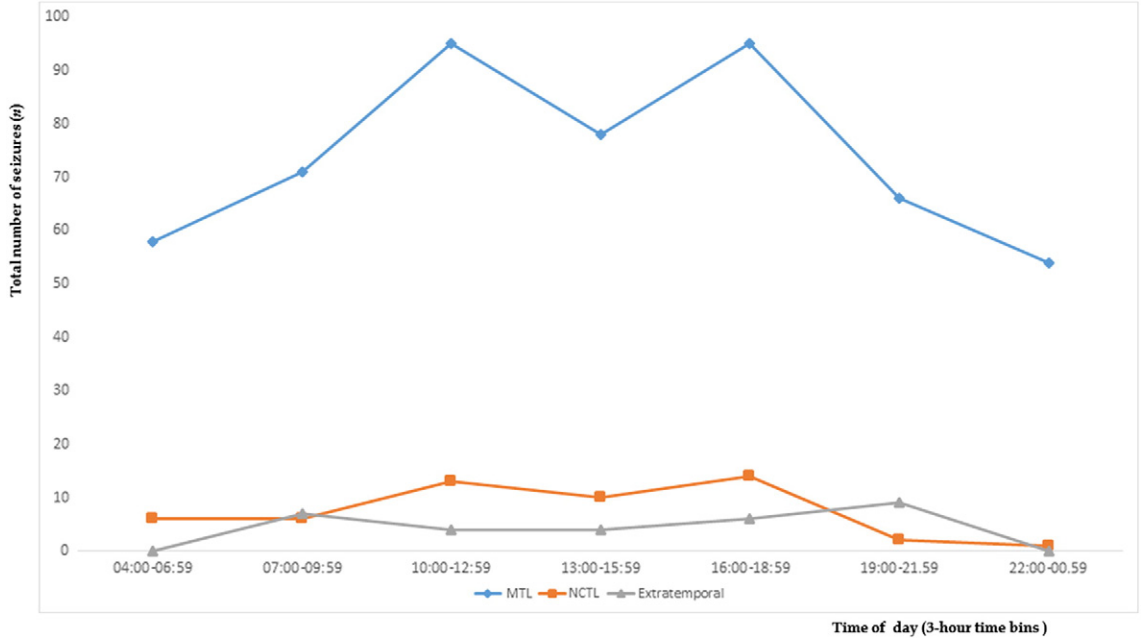

Fig. 1. 24-hour distribution of seizures using 3-hour bins in patients with mesial temporal (MTL), neocortical temporal (NCTL), and extratemporal lobe epilepsy.