Seizure: European Journal of Epilepsy 70 (2019) 90–96

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

The onset of pediatric refractory status epilepticus is not distributed uniformly during the day

Iván Sánchez Fernández[a,b], Marina Gaínza-Lein[a,c], Nicholas S. Abend[d], Marta Amengual-Gual[a,e], Anne Anderson[f], Ravindra Arya[g], J. Nicholas Brenton[h], Jessica L. Carpenter[i], Kevin E. Chapman[j], Justice Clark[a], Raquel Farias-Moeller[k], William Davis Gaillard[i], Tracy A. Glauser[g], Joshua Goldstein[l], Howard P. Goodkin[h], Réjean M. Guerriero[m], Kurt Hecox[k], Michele Jackson[a], Kush Kapur[a], Sarah A. Kelley[n], Eric H.W. Kossoff[n], Yi-Chen Lai[f], Tiffani L. McDonough[o], Mohamad A. Mikati[p], Lindsey A. Morgan[q], Edward J. Novotny[q], Adam P. Ostendorf[r], Eric T. Payne[s], Katrina Peariso[g], Juan Piantino[t], James J. Riviello Jr.[f], Kumar Sannagowdara[k], Carl E. Stafstrom[n], Robert C. Tasker[u], Dmitry Tchapyjnikov[p], Alexis A. Topjian[v], Alejandra Vasquez[a], Mark S. Wainwright[q], Angus Wilfong[w], Korwyn Williams[w], Tobias Loddenkemper[a,*], on behalf of the Pediatric Status Epilepticus Research Group

[a] Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
[b] Department of Child Neurology, Hospital Sant Joan de Déu, Universidad de Barcelona, Barcelona, Spain
[c] Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile
[d] Division of Neurology, The Children's Hospital of Philadelphia, The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[e] Pediatric Neurology Unit, Department of Pediatrics, Hospital Universitari Son Espases, Universitat de les Illes Balears, Palma, Spain
[f] Section of Neurology and Developmental Neuroscience, Department of Pediatrics, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA
[g] Division of Pediatric Neurology, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA
[h] Department of Neurology and Pediatrics, University of Virginia Health System, Charlottesville, VA, USA
[i] Center for Neuroscience, Children's National Medical Center, George Washington University School of Medicine and Health Sciences, Washington, DC, USA
[j] Departments of Pediatrics and Neurology, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA
[k] Department of Pediatric Neurology, Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, WI, USA
[l] Ruth D. & Ken M. Davee Pediatric Neurocritical Care Program, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
[m] Division of Pediatric and Developmental Neurology, Departments of Neurology, Washington University School of Medicine, St. Louis, MO, USA
[n] Department of Neurology, Johns Hopkins Hospital, Johns Hopkins University, Baltimore, MD, USA
[o] Division of Child Neurology, Department of Neurology, Columbia University Medical Center, Columbia University, New York, NY, USA
[p] Division of Pediatric Neurology, Duke University Medical Center, Duke University, Durham, NC, USA
[q] Departments of Pediatrics and Neurology, Seattle Children's Hospital, University of Washington, and Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA, USA
[r] Department of Neurology, Nationwide Children's Hospital, Ohio State University, Columbus, OH, USA
[s] Department of Neurology, Mayo Clinic, Mayo Clinic School of Medicine, Rochester, MN, USA
[t] Department of Neurology, Doernbercher Children's Hospital, Oregon Health & Science University, Portland, OR, USA
[u] Department of Neurology, Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
[v] Division of Critical Care Medicine, The Children's Hospital of Philadelphia, The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[w] Barrow Neurological Institute, Phoenix Children's Hospital, Department of Pediatrics, University of Arizona School of Medicine, Phoenix, AZ, USA

ARTICLE INFO

Keywords:
24-hour rhythms
Chronobiology
Epilepsy
Pediatric
Status epilepticus

ABSTRACT

Purpose: To evaluate whether the onset of pediatric refractory status epilepticus (rSE) is related to time of day. *Method:* We analyzed the time of day for the onset of rSE in this prospective observational study performed from June 2011 to May 2019 in pediatric patients (1 month to 21 years of age). We evaluated the temporal distribution of pediatric rSE utilizing a cosinor analysis. We calculated the midline estimating statistic of rhythm (MESOR) and amplitude. MESOR is the estimated mean number of rSE episodes per hour if they were evenly

* Corresponding author at: Harvard Medical School, Division of Epilepsy and Clinical Neurophysiology, Fegan 9, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA.
E-mail address: tobias.loddenkemper@childrens.harvard.edu (T. Loddenkemper).

https://doi.org/10.1016/j.seizure.2019.06.017
Received 16 August 2018; Received in revised form 10 June 2019; Accepted 12 June 2019

distributed. Amplitude is the difference between MESOR and maximum rSE episodes/hour, or between MESOR and minimum rSE episodes/hour. We also evaluated the temporal distribution of time to treatment.
Results: We analyzed 368 patients (58% males) with a median (p_{25} – p_{75}) age of 4.2 (1.3–9.7) years. The MESOR was 15.3 (95% CI: 13.9–16.8) and the amplitude was 3.2 (95% CI: 1.1–5.3), $p = 0.0024$, demonstrating that the distribution is not uniform, but better described as varying throughout the day with a peak in the morning (11am–12 pm) and trough at night (11 pm–12 am). The duration from rSE onset to application of the first non-benzodiazepine antiseizure medication peaked during the early morning (2am–3 am) with a minimum during the afternoon (2 pm–3 pm) ($p = 0.0179$).
Conclusions: The distribution of rSE onset is not uniform during the day. rSE onset shows a 24-h distribution with a peak in the mid-morning (11am–12 pm) and a trough at night (11 pm-12am).

1. Introduction

Status epilepticus (SE) is one of the most common neurological emergencies in children, with an incidence of 17–23/100,000 per year [1–4]. Pediatric SE is associated with a short-term mortality of 0–3% [1,4–8] which is as high as 20–40% [9] in refractory SE (rSE). One of the most disabling features of epilepsy and SE is the apparently unpredictable timing of seizure occurrence [10]. However, seizures, and presumably SE, follow day and multiday rhythms [10–13].

A growing body of evidence suggests that seizures cluster at specific times following a diurnal and nocturnal distribution, with an overall peak during the day and a trough at night [14,15]. The diurnal and nocturnal distribution of seizures is sometimes specific for some subgroups defined by seizure semiology, periods of wakefulness or sleep [14,16], specific location of seizure onset in the brain [14,16,17], and even specific to the individual patient [18]. In contrast to the relatively well-described circadian patterns of seizure occurrence, there is limited data on whether SE and rSE follow diurnal patterns [12]. In particular, the only study on the daily distribution of SE dichotomizes its occurrence in day and night [12]. SE and rSE are acute emergencies that require abundant resources in both out of hospital (initial treatment by caregiver, ambulances) and in hospital (frequent management in the intensive care unit) settings. While it is currently unknown if there are peaks and troughs of SE occurrence during certain time intervals during the day, such information is important to optimize resources. Also, delays in treatment administration for rSE are frequent [19] but there are no data on whether there are diurnal variations in this pattern.

The current study aimed to address this gap in knowledge by describing the distribution in the time of day of pediatric rSE onset. The secondary aim was to describe the diurnal variations in time to treatment (time from rSE onset to administration of the first benzodiazepine (BZD) and time from rSE onset to administration of the first non-benzodiazepine ASM (non-BZD ASM)). We hypothesized that rSE occurrence follows a distribution that varied with the time of day.

2. Patients and methods

2.1. Standard protocol approvals, registrations, and patient consents

The study was approved by the Institutional Review Board at each participating institution. Written informed consent was obtained from parents or guardians.

2.2. Study design

We performed a prospective observational study at major pediatric hospitals in the United States within the pediatric Status Epilepticus Research Group (pSERG) [20]. This multicenter network of hospitals collects prospective data on patients with rSE with the overall goal of delineating strategies for improving the management and eventually the outcome of children with SE [20]. For the purposes of this study, rSE was considered when SE continued after administration of at least two antiseizure medications (ASMs), including at least one non-BZD ASM or the use of a continuous infusion to treat SE.

2.3. Patients

Inclusion criteria were: 1) age 1 month to 21 years; 2) admission to a pSERG center between June, 1, 2011 and May, 1, 2019; and 3) focal or generalized convulsive seizures at onset that continued after administration of at least two ASMs, including at least one non-BZD ASM or the use of a continuous infusion to treat SE. Exclusion criteria were: 1) non-convulsive SE detected on electroencephalogram (EEG) without convulsive seizures at onset; 2) non-convulsive SE with motor manifestations limited to infrequent myoclonic jerks; 3) no data on the time of SE onset; and 4) clinical presentation, EEG findings, and follow-up data consistent with psychogenic non-epileptic seizures. The definition of rSE is a consensus definition based on the approach that SE should be considered refractory after failure of an initial BZD followed by another class of ASM [20]. The definition of rSE was based on the failure to respond to medications as clinically evaluated. Although the response to medications was evaluated both clinically and with EEG in some patients later in the course of SE, most patients were considered refractory at a point of their SE when EEG was not yet placed. If more than one episode of rSE occurred during the study period, only the first episode was included.

2.4. Outcome variables

The primary outcome of this study was the distribution of rSE onset within the 24 h of a day. Times of rSE onset were considered within the hour they occurred so that 1:00pm to 1:59pm were ascribed to 1 pm, and 2:00pm to 2:59pm were ascribed to 2 pm. As a sensitivity analysis, we also evaluated the assignment of hour so that 12:30pm to 1:29pm were ascribed to 1 pm, and 1:30pm to 2:29pm were ascribed to 2 pm. Although the pSERG centers are distributed throughout several time zones in North America, all times were local times. As secondary outcomes we evaluated the time from rSE onset to administration of the first BZD and the time to administration of the first non-BZD ASM as markers of timely management of rSE. The time to ASM administration was based on information from families and emergency medical services (EMS) for out of hospital onset, and from provider information and medical records once the patient was in the hospital. Data was collected with a standardized data acquisition tool and entered into an electronic database hosted by Cincinnati Children's Hospital Medical Center. Further information on the pSERG consortium are detailed elsewhere [20].

2.5. Statistical analysis

Demographic and clinical characteristics were summarized with descriptive statistics. We tested whether the distribution of rSE onsets followed a uniform distribution with a Kolmogorov-Smirnov test. Subsequently, we evaluated whether the distribution followed a circadian distribution with a

cosinor analysis. The cosinor test is significant when the variance explained by the circadian model is large compared with the variance that remains unexplained [21]. We used a cosinor analysis of cross-sectional sampling. The period assumed for this cosinor analysis was 24 h, and this period was chosen as patients are exposed to daily time cues. A conventional alpha level of 0.05 was considered to be statistically significant for all analyses. All statistical analyses were performed with R (version 3.4.1): a language and environment for statistical computing (R Core Team (2015). R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/) [22] with RStudio [23], and the plyr [24], gdata [25], gmodels [26], cosinor [27], ggplot2 [28], and plotly [29] packages. The full code for analysis with the corresponding results and interactive figures can be found at File e-1 (available at https://github.com/IvanSanchezFernandez/pSERGCircadian and at https://zenodo.org/badge/latestdoi/144916731) which contains the analysis of the de-identified patients.

3. Results

3.1. Study population

We enrolled 368 patients (58% males) with a median (p_{25}-p_{75}) age of 4.2 (1.3–9.7) years of whom 7 (1.9%) were 18 year-old or older. As per our inclusion criteria, we only considered the first rSE episode for each patient, and therefore 368 rSE onsets were included. Table 1 summarizes the main demographic and clinical features of the cohort.

3.2. 24-h distribution of SE

The visual evaluation of the distribution of rSE suggests a day and night rhythm with a peak onset before noon and a trough of onsets at night, although with some variability from that pattern in individual hours of the day (Fig. 1). The Kolmogorov-Smirnov test rejected the null hypothesis of a uniform distribution for the rSE onsets ($p = 0.0061$). In the cosinor analysis, the midline estimating statistic of rhythm (MESOR) –the estimated mean number of rSE onsets per hour if evenly distributed— was 15.3 (95% CI: 13.9–16.8) rSE onsets per hour. The amplitude of this diurnal rhythm was 3.2 (95% CI: 1.1–5.3) rSE onsets per hour ($p = 0.0024$). The null hypothesis was that the amplitude of the 24-h variation of rSE onsets per hour is 0: there is no circadian variation and the distribution is uniform. This null hypothesis was rejected and the mean expected difference in rSE onsets per hour between the peak number of rSE onsets in the mid-morning (11am–12 pm) and the trough number of rSE onsets at night (11 pm–12 am) was 6.4 rSE onsets per hour (Fig. 2).

3.3. Sensitivity analysis

Assigning the hour so that 1:30pm to 2:29pm were ascribed to 2 pm, and 2:30pm to 3:29 pm were ascribed to 3 pm, etc., the Kolmogorov-Smirnov test rejected the null hypothesis of a uniform distribution for the rSE onsets ($p = 0.0135$). In the cosinor analysis with these re-defined hours the MESOR was 15.3 (95% CI: 13.9–16.8) rSE onsets per hour. The amplitude of this diurnal rhythm was 3.4 (95% CI: 1.4–5.5) rSE onsets per hour ($p = 0.0011$). The null hypothesis was that the amplitude of the 24-h variation of rSE onsets per hour is 0: there is no circadian variation and the distribution is uniform. This null hypothesis was also rejected in this sensitivity analysis and the mean expected difference in rSE onsets per hour between the peak number of rSE onsets in the mid-morning (11am–12 pm) and the trough number of rSE onsets at night (11 pm–12 am) was 6.8 rSE onsets per hour (Fig. 3).

3.4. Subgroup comparison

We compared patients with and without a history of any neurologic disease (including epilepsy), patients with and without a history of epilepsy, and patients with rSE onset out of the hospital or in the hospital. This study was not powered sufficiently to detect a significant difference in the distribution of rSE within these subgroups or differences in the amplitude or acrophase (time at which the peak of a rhythm occurs) between subgroups (Figs. 4A–C and File e-1 available at https://github.com/IvanSanchezFernandez/pSERGCircadian and at https://zenodo.org/badge/latestdoi/144916731)

3.5. Time to administration of the first BZD and the first non-BZD ASM

As secondary outcome, the median (p_{25}-p_{75}) time elapsed since rSE onset to administration of the first BZD was 16.5 (5–45) minutes with a distribution that was not different than that of a uniform distribution ($p = 0.4779$) (Figure e-1). The median (p_{25}–p_{75}) time elapsed from rSE onset to administration of the first non-BZD ASM was 66 (35–150) minutes. Its distribution was different than that of a uniform distribution ($p = 0.0179$), demonstrating a peak in time to treatment around 2am–3 am and a trough in time to treatment around 2pm–3 pm (Figure e-2 and File e-1 available at https://github.com/IvanSanchezFernandez/pSERGCircadian and at https://zenodo.org/badge/latestdoi/144916731).

4. Discussion

The distribution of pediatric rSE onset is better explained by a diurnal pattern that varies with a peak in the morning around 11am-12 pm and a trough at night around 11 pm-12am than by a uniform distribution during the day. Similarly, we found that the time lapse from rSE onset to administration of the first non-BZD ASM peaked during the night around 2am–3 am with the shortest duration to treatment occurring in the afternoon around 2 pm–3 pm. The time lapse from rSE onset to administration of the first BZD was not statistically significantly different than that of a uniform distribution.

4.1. Clinical relevance

In our series, with a mean number of 15.3 onsets of rSE per hour,

Table 1
Demographic and clinical characteristics.

Age at SE in years	Median (p_{25}–p_{75})	4.2 (1.3–9.7)
Gender	Male	213 (57.9%)
	Female	155 (42.1%)
Race	White	237 (64.4%)
	African-American	71 (19.3%)
	Asian	11 (3%)
	Arabic	10 (2.7%)
	Hawaiian/Pacific	1 (0.3%)
	Unknown/not reported	37 (10.1%)
Ethnicity	Hispanic or Latino	66 (17.9%)
	Non-Hispanic or Latino	269 (73.1%)
	Unknown / not reported	33 (9%)
Medical history*	DD/ID	186 (50.5%)
	Cerebral palsy	39 (10.6%)
	SE with fever	40 (10.9%)
	History of epilepsy	182 (49.5%)
	History of SE	69 (18.8%)
	No past neurological history	120 (32.6%)
Duration of SE in minutes	Median (p_{25}-p_{75})	122 (60-283)
Onset of the episode	Out of the hospital	258 (70.1%)
	In hospital	110 (29.9%)
Type of SE	Continuous	116 (31.5%)
	Intermittent	252 (68.5%)

Legend: %: Percentage. DD: Developmental delay. ID: Intellectual disability. SE: Status epilepticus. p_{25}–p_{75}: percentiles 25th and 75th.

* Percentages for past medical history do not sum up to 100% as several patients have more than one condition.

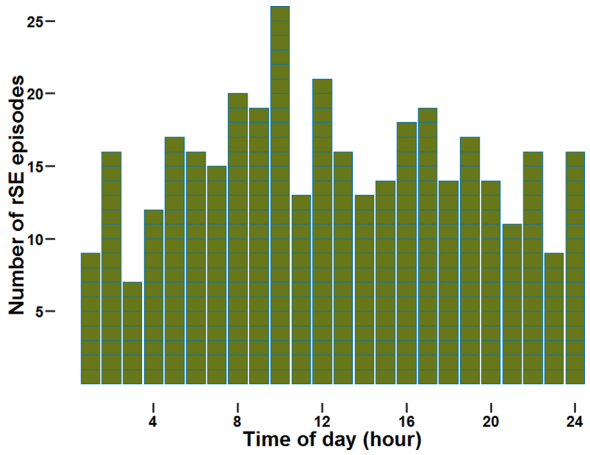

Fig. 1. Graph of the distribution of rSE onsets during the day. Distribution of rSE onsets in 1-h intervals. The visual examination of the distribution of rSE onsets suggests a 24-h rhythm with a peak at approximately 11am −12 pm and a trough at approximately 11 pm −12 am.
Legend: rSE: refractory status epilepticus.

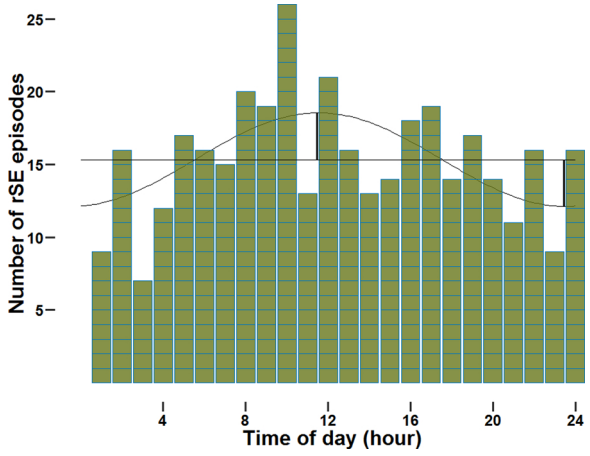

Fig. 2. Graph of the circadian distribution of rSE onsets during the day superimposed on the bar graph. The figure shows the MESOR (horizontal line), the amplitude (vertical lines at the estimated peak around 11am −12 pm and trough around 11 pm −12 am) and the fit curve of the cosinor model.
Legend: MESOR: midline estimating statistic of rhythm. rSE: refractory status epilepticus.

there was a difference of 6.4 rSE onsets per hour between the peak in the morning, and the trough at night. For a 24-h MESOR of 15.3 rSE onsets per hour, this represents a change of 42% throughout the day (21% over the MESOR at the peak and 21% below the MESOR at the trough). This change in the frequency of pediatric rSE occurrence during the day may help organize SE-specific EMS resources as well as patient monitoring in a more rational and data-driven way. There is a growing body of literature showing that the occurrence of seizures is not as unpredictable as it seems [30] and there is a growing interest in recording and forecasting the time of seizure occurrence [31,32]. Our data shows that there are peak times of rSE occurrence and this may help EMS and emergency room personnel to be particularly prepared for SE at these peak hours. In addition, these data may fuel the evaluation of diurnal and nocturnal rhythms of different types of SE. We compared subgroups of patients with and without a history of any neurologic disease (including epilepsy), patients with and without a history of epilepsy, and patients with rSE onset out of the hospital or in the hospital, but we did not find differences. Defining specific time windows of higher SE susceptibility in different types of patients may help tailor differential dosing so that higher medication doses coincide

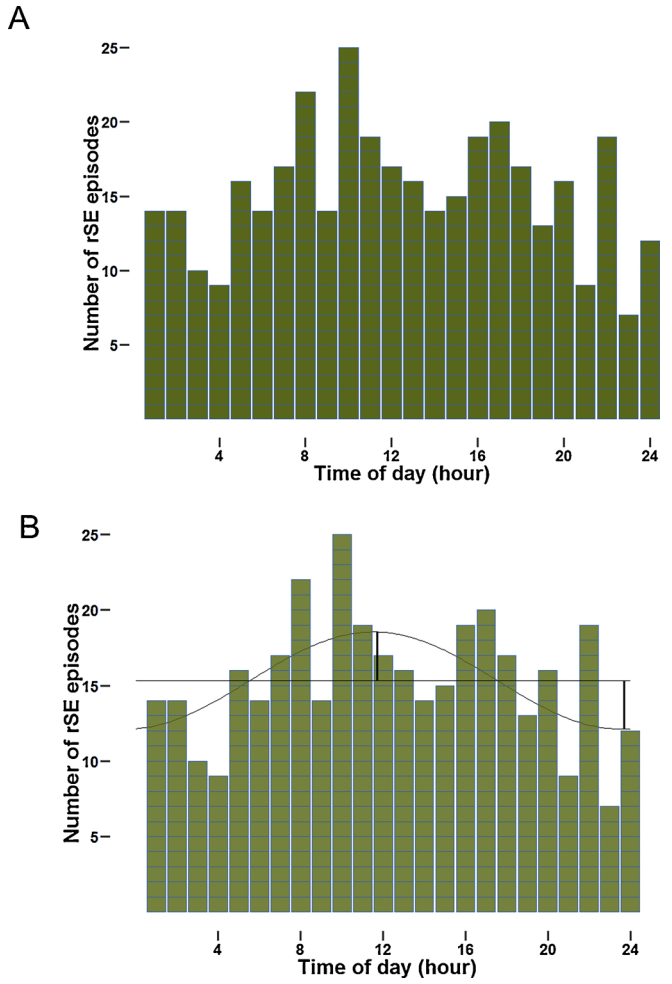

Fig. 3. Graph of the distribution of rSE onsets during the day considering the alternative assignment of hours. Hours are assigned so that 12:30pm to 1:29pm were ascribed to 1 pm, and 1:30pm to 2:29pm were ascribed to 2 pm, etc. A. Bar graph. B. Bar graph with superimposed cosinor model.
Legend: rSE: refractory status epilepticus.

with times of greater seizure and SE susceptibility [13,33,34]. Increased ASM levels may be protective at the times when SE is more likely to occur in susceptible patients. Individual rhythms may further tailor this approach to the individual patient.

4.2. 24-h distribution of seizures

One of the most disabling features of epilepsy is the unpredictable timing of seizure occurrence [10], especially for patients out of the hospital where rapid access to care is not always readily available. A growing body of evidence shows that seizures tend to cluster at specific times during the day [14–16,35,36]. In a series of 176 patients (100 adults and 76 children), seizures peaked between 11am and 5 pm and reached a trough between 11 pm and 5am [14]. A study of 96 patients with 1350 focal onset seizures showed a peak between 12 pm and 5 pm and a trough between 1am and 6am [15]. When seizures are analyzed individually by lobe of origin or seizure semiology, each seizure type has its own specific 24-h rhythm [16,35,36]. In a series of 131 adults who underwent intracranial EEG monitoring and had 669 seizures in total, occipital seizures peaked between 4 pm and 7 pm, parietal seizures between 4am and 7am, frontal seizures between 4am and 7am, and mesial temporal lobe seizures showed two peaks between 4 pm and 7 pm hours and between 7am and 10am [35]. In another series, 15 patients with 41 temporal lobe seizures had their peak frequency

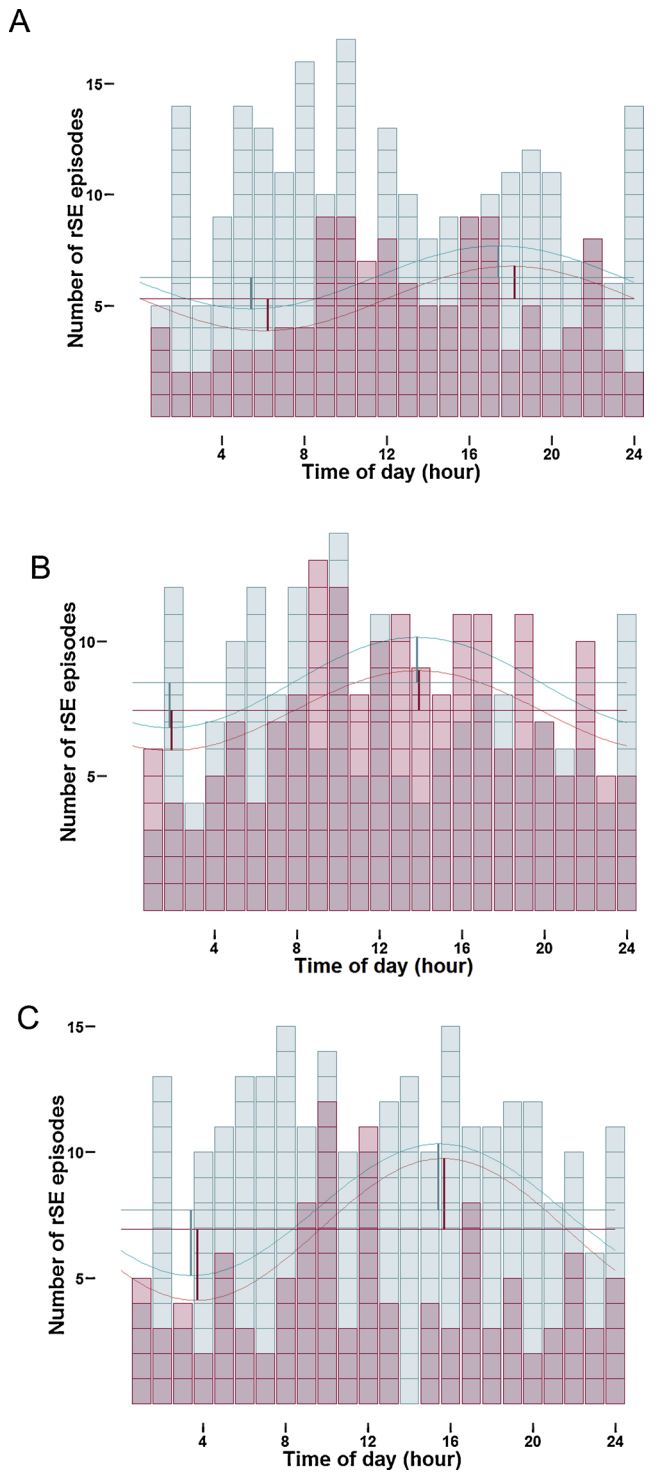

Fig. 4. Graph of the circadian distribution of rSE onsets during the day. A. Comparison of patients with (blue) and without (red) a history of a prior neurological condition including epilepsy. B. Comparison of patients with (blue) and without (red) a history of epilepsy with or without other conditions. C. Comparison of patients with out of hospital onset (blue) and in hospital onset (red) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).
Legend: rSE: refractory status epilepticus.

between 3 pm and 7 pm and 11 patients with 49 extratemporal lobe seizures had their peak frequency between 7 pm and 11 pm; in addition, temporal lobe seizures occurred less frequently during sleep than extratemporal seizures [36]. Similarly, a series of 380 children with 1008 seizures described the specific circadian distribution for each seizure type and also showed that the sleep-wakefulness dichotomy was more predictive of seizure occurrence than the night-day dichotomy [16]. Similar to our findings, in a study of 134 patients with seizures detected with ambulatory intracranial electrodes electrographic seizures of neocortical origin showed a peak occurrence during the night and early morning hours [37]. In summary, seizure occurrence appears to be related to 24-h rhythms and the sleep-wakefulness pattern, although there are more data on the 24-h distribution of seizures than on their distribution out of wakefulness or sleep. Differential occurrence of seizures and SE during the day may allow optimization of treatment strategies targeting periods of greater seizure susceptibility with higher doses of ASMs [13,33], or improved escalation of ASM dosing.

4.3. 24-h distribution of SE

In contrast to the extensive and detailed literature on the circadian distribution of seizures, there are very limited data on the 24-h distribution of SE. In an analysis of a large patient-entered electronic seizure diary with dichotomized SE onset into day and night, clusters of seizures including SE occurred more frequently during the daytime, although SE occurred more frequently during the night in children [12]. In contrast, our data with more granularity on the specific hours of rSE onset show that rSE onsets peak during the morning and are less frequent at night. There are no comparable studies on SE occurrence during the day, but the daily peaks and nightly troughs are roughly similar to those from studies on the day and nighttime distribution of seizures [14,15]. The 24-h distribution was shifted towards earlier times in rSE than in non-SE seizures, with a peak rSE occurrence between 11 am and 12 pm – as compared to a peak between 11 am and 5 pm [14] or between 12 pm and 5 pm [15] for seizures— and a trough between 11 pm and 12 am – as compared to a trough between 11 pm and 5 am [14] or between 1am and 6am for seizures [15]. It remains unknown as to what causes this shift towards earlier times in rSE compared to shorter seizures. We speculate that a different mechanism underlies evolution into rSE and termination of isolated shorter seizures. The 24-h periodicity of epilepsy and its relation to sleep-wake cycles are not well understood. The suprachiasmatic nucleus, located in the hypothalamus, is the master pacemaker in the central nervous system, influencing a complex network of oscillators distributed centrally and peripherally and influenced by hormonal rhythms [13,38]. If rSE and shorter seizures have different 24-h rhythms, this may point towards different rhythmic oscillators, or day-night variation of excitatory and inhibitory balance, influencing their onset and termination. Alternatively, this shift in day and nighttime occurrence may simply reflect a different composition of seizure types –with their different underlying 24 h rhythms— that evolve into rSE, with the seizure types more likely to evolve into rSE having an earlier time distribution during the day or simply higher detection rate of longer seizures and SE than of shorter seizures during the night. The evolution of seizure semiology over different day and night periods has been described previously [39]. Although seizure semiology evolved in some of our patients, we do not have sufficient detail and patient numbers to study the pattern of evolution over different periods of the day and night in this series. Future series with larger samples of SE onsets will help clarify the circadian rhythms of different subtypes of SE.

4.4. 24-h distribution of time to treatment

Delays to treatment administration for the first non-BZD ASM peaked at night. The time to the first BZD did not differ from a uniform distribution, but the time to the first non-BZD ASM suggested that treatment stages that require multiple steps (administration of a non-BZD ASM after having received one or more BZDs) are delayed at night. This finding probably reflects that most hospitals have fewer clinicians and, in particular, fewer pediatric neurologists available during the

night. However, to the best of our knowledge, this is the first study evaluating the delay in time to treatment for SE across day and night. These findings may be limited by the presence of outliers in the distributions, for which cosinor analysis is sensitive to. That is, contrary to the main analysis of distribution of time of rSE occurrence, in the analysis of time to treatment there were some outlier observations that may skew the analysis. Cosinor analysis is a parametric method that is sensitive to outliers and our current numbers did not allow us to perform an equivalent non-parametric circadian analysis. Future studies with larger populations will help clarify this clinically relevant issue. However, it is interesting by itself that these unusually long delays occurred mostly at night. If treatment delays are longer at night with most outliers occurring at night then these findings may also help target quality improvement measures to improve treatment delays at night. Patients are at greater risk of SUDEP at night, and nighttime supervision or monitoring may potentially be an option to help prevent complications from seizures [40].

4.5. Strengths and weaknesses

We enrolled patients admitted to large tertiary care hospitals. Episodes of SE that occur in the community and never reach large hospitals could not have been studied with this approach. Therefore, our patient population is not necessarily representative of all children with SE but of pediatric rSE treated at large centers. This selection bias may limit the generalizability of results. On the other hand, a multicenter study including hospitals with a large volume of patients is necessary in order to gather a large number of SE episodes with detailed information on time of onset. The number of rSE episode onsets in this study allows an estimation of their global circadian distribution, which is robust to sensitivity analysis on how to assign hours, but it is not sufficient to individualize specific circadian distributions in particular subgroups of rSE types. Due to insufficient numbers, we did not compare patients with rSE onset in the ICU versus patients with rSE onset out of the ICU. The number of patients in the analysis did not permit performance of two-peak hypotheses. Fig. 3B suggests a major peak around 11am-12 pm and a minor peak at around 6pm-7 pm, but the number of rSE episodes did not allow us to model this aspect. Potential underlying etiologies of these two potential peaks are unclear, but may be related to the morning and afternoon peaks of cortisol or differences in the sleep-wakefulness cycle that we cannot evaluate with the present data. Although daylight saving and different months during the year may have influenced the circadian rhythms the amount of data did not allow adjusting for these factors. The dataset did not allow correction for other factors influencing the circadian distribution of rSE onsets such as the times of scheduled ASMs, stress, infections, or menstruation. We require the onset of rSE to be observed, thus, it is possible that rSE onsets are most often observed during the day than during the night. Episodes with unknown time of onset are not enrolled in pSERG as this is an exclusion criterion, but having an unknown time of onset may happen more frequently overnight with the potential to select non-consecutive patients. The possibility of patients with rSE being admitted more frequently during the day than at night is unlikely as rSE is a severe condition which is almost always treated in an ICU. Further studies may need to evaluate whether the distribution is consistent or whether there is a selection bias. It can be speculated that the distribution of rSE may potentially reflect worse compliance with regular medication in the morning than at night, although we have no data to support that hypothesis.

Times were assessed based on family and EMS information for out of hospital onset and from provider information and hospital records once in the hospital. As this method of data acquisition may introduce an amount of information and recall bias, we cross-referenced information on times with families, EMS, nurses, and medication administration records when available to reduce bias. The cosinor analysis is sensitive to extreme values because it relies on the mean rather than the median. However, there were no extreme outliers in the number of rSE onsets per hour in our sample.

This study evaluated the influence of the time of day on rSE occurrence. The 24-h distribution of seizures may partially reflect the influence of sleep-wakefulness cycles on rSE occurrence, but our database did not collect information on whether rSE onsets occurred during wakefulness or during sleep. Although it is likely that most seizures during the night came out of sleep, we do not have that data as pSERG is not currently collecting that variable. The current data did not permit evaluation of multi-day rhythms such as seasonal rhythms, which may play a relevant influence in the distribution of seizure and SE occurrence [11]. This study did not collect information on the timing of ASM and their doses prior to rSE. The current study will fuel future evaluations of the circadian distribution of SE that will collect information on sleep-wakefulness stage at SE onset.

5. Conclusions

The onset of pediatric rSE does not follow a uniform distribution, but a pattern with a peak in the morning and a trough at night. Escalation of treatment from BZDs to non-BZD ASMs also was more delayed in rSE starting at night.

Disclosures

ISF is funded by the Epilepsy Research Fund and was funded by Fundación Alfonso Martín Escudero and the HHV6 Foundation. MG-L reports no disclosures. NSA reports no disclosures. MA-G is funded by a grant for the study of status epilepticus from “Fundación Alfonso Martín Escudero”. AA reports no disclosures. RA reports no disclosures. JNB reports no disclosures. JLC reports no disclosures. KEC reports no disclosures. JC reports no disclosures. RF-M reports no disclosures. WDG is an editor for Epilepsy Research. TAG is funded by NIH grants 2U01-NS045911, U10-NS077311, R01-NS053998, R01-NS062756, R01-NS043209, R01-LM011124, and R01-NS065840. He has received consulting fees from Supernus, Sunovion, Eisai, and UCB. He also serves as an expert consultant for the US Department of Justice and has received compensation for work as an expert on medico-legal cases. He receives royalties from a patent license. JLG reports no disclosures. HPG reports no disclosures. RMG reports no disclosures. KH reports no disclosures. MCJ reports no disclosures. KK reports no disclosures. SAK reports no disclosures. EHWK reports no disclosures. YCL reports no disclosures. TLM reports no disclosures. MAM reports no disclosures. LM reports no disclosures. EJN reports no disclosures. APO reports no disclosures. ETP reports no disclosures. KP reports no disclosures. JP reports no disclosures. JJR is a member of a data safety monitoring board for GW Pharmaceuticals. His spouse is an editor for Uptodate. KS reports no disclosures. CES has received consultant fees from Mallinckrodt and speaker fees from Nutricia. RCT reports no disclosures. DT reports no disclosures. AAT reports no disclosures. AV reports no disclosures. MSW serves as a scientific consultant and on the clinical advisory board for Sage Therapeutics. AW receives research funding from Novartis, Eisai, Pfizer, UCB, Acorda, Lundbeck, GW Pharma, Upsher-Smith, and Zogenix and receives publication royalties from Uptodate. KW reports no disclosures. TL serves on the Council (and as President) of the American Clinical Neurophysiology Society (active), on the American Board of Clinical Neurophysiology (active), served as an Associate Editor for Seizure, served on the Laboratory Accreditation Board for Long Term (Epilepsy and Intensive Care Unit) Monitoring, and serves as an Associate Editor for Wyllie’s Treatment of Epilepsy 6th and 7th edition. He is part of patent applications and license agreements to detect and predict seizures, and to manage and diagnose epilepsy, and future revenue from these scientific contributions cannot be ruled out. TL is co-inventor of the TriVox Health technology. TL and Boston Children’s Hospital might receive financial benefits in the form of compensation in the future. He received research support from the NIH,

Epilepsy Research Fund, the Epilepsy Foundation of America, the Epilepsy Therapy Project, the Pediatric Epilepsy Research Foundation, Lundbeck, Eisai, Upsher-Smith, Sunovion, Mallinckrodt, Empatica, Sage, and Pfizer. He served as a consultant for Zogenix, Upsher Smith, Amzell, Sunovion, Engage, UCB, Advance Medical, and Grand Rounds. He performs video electroencephalogram long-term and ICU monitoring, electroencephalograms, and other electrophysiological studies at Boston Children's Hospital and affiliated hospitals and bills for these procedures and he evaluates pediatric neurology patients and bills for clinical care. He has received speaker honorariums from national societies including the AAN, AES and ACNS, and for grand rounds at various academic centers. His wife, Dr. Karen Stannard, is a pediatric neurologist and she performs video electroencephalogram long-term and ICU monitoring, electroencephalograms, and other electrophysiological studies and bills for these procedures and she evaluates pediatric neurology patients and bills for clinical care.

Acknowledgements

This study and consortium was funded by the Epilepsy Foundation of America (EF-213583, Targeted Initiative for Health Outcomes), by American Epilepsy Society/Epilepsy Foundation of America Infrastructure Awards, the Pediatric Epilepsy Research Foundation, and the Epilepsy Research Fund.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2019.06.017.

References

[1] Chin RF, Neville BG, Peckham C, Bedford H, Wade A, Scott RC, et al. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet 2006;368:222–9.
[2] Coeytaux A, Jallon P, Galobardes B, Morabia A. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). Neurology 2000;55:693–7.
[3] Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Incidence of status epilepticus in Rochester, Minnesota, 1965–1984. Neurology 1998;50:735–41.
[4] Singh RK, Stephens S, Berl MM, Chang T, Brown K, Vezina LG, et al. Prospective study of new-onset seizures presenting as status epilepticus in childhood. Neurology 2010;74:636–42.
[5] DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology 1996;46:1029–35.
[6] Loddenkemper T, Syed TU, Ramgopal S, Gulati D, Thanaviratananich S, Kothare SV, et al. Risk factors associated with death in in-hospital pediatric convulsive status epilepticus. PLoS One 2012;7:e47474.
[7] Maytal J, Shinnar S, Moshe SL, Alvarez LA. Low morbidity and mortality of status epilepticus in children. Pediatrics 1989;83:323–31.
[8] Wu YW, Shek DW, Garcia PA, Zhao S, Johnston SC. Incidence and mortality of generalized convulsive status epilepticus in California. Neurology 2002;58:1070–6.
[9] Raspall-Chaure M, Chin RF, Neville BG, Scott RC. Outcome of paediatric convulsive status epilepticus: a systematic review. Lancet Neurol 2006;5:769–79.
[10] Quigg M. Circadian rhythms: interactions with seizures and epilepsy. Epilepsy Res 2000;42:43–55.
[11] Baud MO, Kleen JK, Mirro EA, Andrechak JC, King-Stephens D, Chang EF, et al. Multi-day rhythms modulate seizure risk in epilepsy. Nat Commun 2018;9:88.
[12] Goldenholz DM, Rakesh K, Kapur K, Gainza-Lein M, Hodgeman R, Moss R, et al. Different as night and day: patterns of isolated seizures, clusters, and status epilepticus. Epilepsia 2018;59:e73–7.
[13] Loddenkemper T, Lockley SW, Kaleyias J, Kothare SV. Chronobiology of epilepsy: diagnostic and therapeutic implications of chrono-epileptology. J Clin Neurophysiol 2011;28:146–53.
[14] Hofstra WA, Grootemarsink BE, Dieker R, van der Palen J, de Weerd AW. Temporal distribution of clinical seizures over the 24-h day: a retrospective observational study in a tertiary epilepsy clinic. Epilepsia 2009;50:2019–26.
[15] Quigg M, Straume M, Menaker M, Bertram 3rd EH. Temporal distribution of partial seizures: comparison of an animal model with human partial epilepsy. Ann Neurol 1998;43:748–55.
[16] Loddenkemper T, Vendrame M, Zarowski M, Gregas M, Alexopoulos AV, Wyllie E, et al. Circadian patterns of pediatric seizures. Neurology 2011;76:145–53.
[17] Hofstra WA, Spetgens WP, Leijten FS, van Rijen PC, Gosselaar P, van der Palen J, et al. Diurnal rhythms in seizures detected by intracranial electrocorticographic monitoring: an observational study. Epilepsy Behav 2009;14:617–21.
[18] Cook MJ, Karoly PJ, Freestone DR, Himes D, Leyde K, Berkovic S, et al. Human focal seizures are characterized by populations of fixed duration and interval. Epilepsia 2016;57:359–68.
[19] Sánchez Fernández I, Abend NS, Agadi S, An S, Arya R, Brenton JN, et al. Time from convulsive status epilepticus onset to anticonvulsant administration in children. Neurology 2015;84:2304–11.
[20] Sánchez Fernández I, Abend NS, Agadi S, An S, Arya R, Carpenter JL, et al. Gaps and opportunities in refractory status epilepticus research in children: a multi-center approach by the Pediatric Status Epilepticus Research Group (pSERG). Seizure 2014;23:87–97.
[21] Cornelissen G. Cosinor-based rhythmometry. Theor Biol Med Model 2014;11:16.
[22] Team RC. R Core Team. R: a language and environment for statistical computing URL Vienna, Austria: R Foundation for Statistical Computing; 2015https://www.R-project.org/.
[23] Team R. RStudio: integrated development environment for R URL: Boston, MA: RStudio, Inc.; 2016http://www.rstudio.com/.
[24] Wickham H. The split-apply-Combine strategy for data analysis. J Stat Softw 2011;40(1):1–29. URL http://www.jstatsoft.org/v40/i01/.
[25] Warnes GR, Bolker B, Gorjanc G, Grothendieck G, Korosec A, Lumley T, et al. Gdata: various R programming tools for data manipulation. R package version 2.17.0. 2015http://CRAN.R-project.org/package=gdata.
[26] Warnes G, Bolker B, Lumley T, Johnson RC. Gmodels: various R programming tools for model fitting. R package version 2.16.2. 2015. Contributions from Randall C. Johnson are Copyright SAIC-Frederick, Inc. Funded by the Intramural Research Program, of the NIH, National Cancer Institute and Center for Cancer Research under NCI Contract NO1-CO-12400. (12015). http://CRAN.R-project.org/package=gmodels.
[27] Sachs M. Cosinor: tools for estimating and predicting the cosinor model. R package version 1.1. 2014http://CRAN.R-project.org/package=cosinor.
[28] Wickham H. ggplot2: elegant graphics for data analysis URL: New York: Springer-Verlag; 2016http://ggplot2.org.
[29] Sievert C, Parmer C, Hocking T, Chamberlain S, Ram K, Corvellec M, et al. Plotly: create interactive web graphics via' plotly.js'. R package version 4.7.1 URL: 2017https://CRAN.R-project.org/package=plotly.
[30] Karoly PJ, Goldenholz DM, Freestone DR, Moss RE, Grayden DB, Theodore WH, et al. Circadian and circaseptan rhythms in human epilepsy: a retrospective cohort study. Lancet Neurol 2018;17:977–85.
[31] Amengual-Gual M, Ulate-Campos A, Loddenkemper T. Status epilepticus prevention, ambulatory monitoring, early seizure detection and prediction in at-risk patients. Seizure 2018.
[32] Ulate-Campos A, Coughlin F, Gainza-Lein M, Fernandez IS, Pearl PL, Loddenkemper T. Automated seizure detection systems and their effectiveness for each type of seizure. Seizure 2016;40:88–101.
[33] Guilhoto LM, Loddenkemper T, Vendrame M, Bergin A, Bourgeois BF, Kothare SV. Higher evening antiepileptic drug dose for nocturnal and early-morning seizures. Epilepsy Behav 2011;20:334–7.
[34] Ramgopal S, Thome-Souza S, Loddenkemper T. Chronopharmacology of anti-convulsive therapy. Curr Neurol Neurosci Rep 2013;13:339.
[35] Durazzo TS, Spencer SS, Duckrow RB, Novotny EJ, Spencer DD, Zaveri HP. Temporal distributions of seizure occurrence from various epileptogenic regions. Neurology 2008;70:1265–71.
[36] Pavlova MK, Shea SA, Bromfield EB. Day/night patterns of focal seizures. Epilepsy Behav 2004;5:44–9.
[37] Spencer DC, Sun FT, Brown SN, Jobst BC, Fountain NB, Wong VS, et al. Circadian and ultradian patterns of epileptiform discharges differ by seizure-onset location during long-term ambulatory intracranial monitoring. Epilepsia 2016;57:1495–502.
[38] Amengual-Gual M, Sánchez Fernández I, Loddenkemper T. Patterns of epileptic seizure occurrence. Brain Res 2018.
[39] Sánchez Fernández I, Ramgopal S, Powell C, Gregas M, Zarowski M, Shah A, et al. Clinical evolution of seizures: distribution across time of day and sleep/wakefulness cycle. J Neurol 2013;260:549–57.
[40] Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. Neurology 2005;64:1131–3.