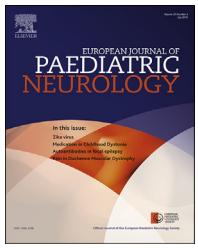
Official Journal of the European Paediatric Neurology Society



Original Article

Sleep-wake distribution and circadian patterns of epileptic seizures in children

Esra Gurkas [a,*], *Ayse Serdaroglu* [b], *Tugba Hirfanoglu* [b], *Ayse Kartal* [b], *Unsal Yılmaz* [b], *Erhan Bilir* [c]

[a] *Department of Pediatric Neurology, Ankara Pediatric & Pediatric Hematology Oncology Training and Research Hospital, Dıskapı, Ankara 06110, Turkey*
[b] *Gazi University Faculty of Medicine, Department of Pediatric Neurology, Ankara, Turkey*
[c] *Gazi University Faculty of Medicine, Department of Neurology, Ankara, Turkey*

ARTICLE INFO

Article history:
Received 30 October 2015
Received in revised form
30 March 2016
Accepted 6 April 2016

Keywords:
Epilepsy
Circadian pattern
Semiology

ABSTRACT

Background: Epilepsy is one of the most common chronic neurologic disorders. Daily periodicity of epileptic seizures has been known for over a century. The diurnal patterns of epileptic seizures have also been observed in studies.
Aim: To investigate the sleep/wake cycle, day/night, and 24-h periodicity of various seizure subtypes and seizure onset localizations in children.
Methods: We analyzed the clinical seizures of 170 consecutive epilepsy patients who underwent video-electroencephalography (EEG) monitoring over the last 5 years. Semiology of the seizures was classified according to the semiological seizure classification. Origin of the seizures was defined by the onset of ictal activity on EEG. Seizures were evaluated in terms of occurrence during the day (06:00–18:00 h) or night (18:00–06:00 h), in wakefulness or in sleep, and within a 3-h time interval throughout 24 h.
Results: A total of 909 seizures were analyzed. Auras, dialeptic, myoclonic, hypomotor, atonic seizures, and epileptic spasms occurred more frequently in wakefulness; tonic, clonic, and hypermotor seizures occurred more frequently in sleep. Auras, dialeptic, and atonic seizures and epileptic spasms occurred more often during daytime; hypermotor seizures occurred more often at night. Generalized seizures were seen most frequently in wakefulness (between 12:00 and 18:00 h); frontal lobe seizures were seen at night and in sleep (between 24:00 and 03:00 h); temporal lobe seizures were seen in wakefulness (between 06:00 and 09:00 h and between 12:00 and 15:00 h); occipital seizures were seen during daytime and in wakefulness (between 09:00 and 12:00 h and between 15:00 and 18:00 h, respectively); parietal seizures were seen mostly during daytime.
Conclusions: Seizures in children occur in specific circadian patterns and in specific sleep/wake distributions depending on seizure onset location and semiology.
© 2016 European Paediatric Neurology Society. Published by Elsevier Ltd. All rights reserved.

* *Corresponding author*. Tel.: +90 312 5969628, +90 533 2500455 (mobile); fax: +90 312 3472330.
E-mail address: esragurkas@yahoo.com (E. Gurkas).
http://dx.doi.org/10.1016/j.ejpn.2016.04.004
1090-3798/© 2016 European Paediatric Neurology Society. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Epilepsy is one of the most common chronic neurologic disorders. Daily periodicity of epileptic seizures has been known for over a century. In 1885, Gowers[1] observed temporal periodicity for seizure occurrence and classified them as diurnal, nocturnal, and diffuse. Diurnal seizures have a tendency to occur upon awakening and in the late afternoon and nocturnal seizures occur mainly at bedtime and in the morning hours before awakening.[2]

Diurnal patterns of epileptic seizures have also been observed in animal and human studies. Studies in rodents with limbic epilepsy showed that spontaneous seizures were more frequent during exposure to light than during darkness.[3–5]

In human studies, the interaction between sleep and seizure has been studied extensively. Patients with frontal lobe epilepsy typically have seizures arising from sleep,[6,7] especially the lighter stages of non-rapid eye movement (NREM) sleep promote seizure.[8,9] Some studies have focused on the relationship between seizure onset localization and seizure occurrence over a 24-h day. In recent years, studies including children and data about the relationship of seizure semiology to circadian rhythm have also been published. These studies are mostly from the United States and Europe. So we decided to perform a large retrospective study in our tertiary epilepsy center in Ankara, Turkey. More knowledge about the diurnal and sleep/wake pattern of epileptic seizures may help us to understand the pathophysiology of the disease and also predicting the timing of seizure can improve the quality of life of the patients with epilepsy. In our study, all children undergoing video-electroencephalography (EEG) monitoring over a 5-year period were included. Our aim was to evaluate the relationship of sleep-wake and the circadian pattern with various semiologic seizure subtypes and seizure localizations and to compare our results with those of the previous studies.

2. Materials and methods

2.1. Patient selection

For this study, we reviewed the charts of 332 consecutive pediatric epilepsy patients undergoing video-EEG monitoring in our epilepsy center between January 2007 and December 2011. Video-EEG monitoring was performed for classification of epilepsy or presurgical evaluation. Patients with clinicoelectrographic seizures occurring during monitorization were included. One hundred and sixty-two patients were excluded due to non-epileptic recorded events, no recorded events or seizures, and missing data. Thus, a total of 170 patients were included.

Antiepileptic medications were tapered in a manner specific to each patient's condition by taking into consideration the baseline seizure frequency, severity, and history of status epilepticus. Patients were permitted to sleep and wake at their own discretion; however, routine inpatient activities such as physician rounds, nursing care, and meal times may have entrained their schedules. Activity was limited to the patient's room because of the confinement imposed by constant connection to the EEG monitoring system. Patients and parents were instructed to press the seizure alarm during occurrence of clinical seizures or suspicious events.

2.2. Continuous video-EEG monitoring

The duration of continuous video-EEG monitoring varied from 1 to 7 days. Scalp EEG recordings were performed using the 10–20 international system of electrode placement along with bilateral anterior temporal electrodes recorded by Nihon-Kohden Neurofax EEG 1200. A total 23 scalp electrodes and ECG electrodes were placed. Video monitoring was performed by closed circuit video cameras. All EEG and video data were saved and later interpreted by 2 epileptologists. After interpretation, all important clinical information was archived.

2.3. Data analysis

All data including EEG and video was evaluated by a well-trained EEG technician and 2 epileptologists. A total of 909 clinical seizures were analyzed. Subclinical EEG seizures were excluded. To prevent the influence of atypically large seizure counts for a few patients on the overall group distribution, we limited the number of seizures for analysis. Ten seizures per patient were randomly selected. The semiology of seizures was evaluated according to Lüders semiological seizure classification.[10] The first semiologic seizure phase was considered for the analysis when seizures evolved into other clinical seizure types. Retrospectively, time onset of seizure and occurrence in wakefulness or sleep were recorded. Data analysis was based on occurrence of seizures during the day (06:00–18:00 h) or night (18:00–06:00 h), in wakefulness or sleep, and within 3-h time blocks throughout a 24-h cycle. Wakefulness or sleep were assessed regardless of the time of the day. In addition, data were also analyzed based on the localization of the epileptogenic focus. Origin of the seizures was defined by coupling the onset of ictal EEG activity with the semiology of the seizures. When the seizures originated from several lobes based on ictal EEG recordings, they were classified as multilobar category.

2.4. Statistical analysis

The nonparametric binomial test was used to test whether numbers of seizures in day or night and wakefulness or sleep were significantly different. The expected probability is 50%, when assuming that seizures occur randomly. The binomial test compares the observed percentage in the study to the expected percentage. The binomial test can be used when there are only two categories. To analyze the seizure distribution within 3-h time blocks, the 24-h day was divided into 8 bins. The time bins were 00:00–03:00 h (I), 03:00–06:00 h (II), 06:00–09:00 (III), 09:00–12:00 h (IV), 12:00–15:00 h (V), 15:00–18:00 h (VI), 18:00–21:00 h (VII), 21:00–24:00 h (VIII). The non-parametric chi square test was used to test whether numbers of seizures within 3-h time blocks were significantly different. The expected probability is 12.5%, when assuming that seizures occur randomly. The non-parametric chi square test also compares between the observed and the expected

percentage. The Statistical Package for the Social Sciences version 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Significance was set at p-values of <0.001, <0.01 and <0.05.

3. Results

3.1. Descriptive data of patients and seizures

Over a 5-year period, 170 patients (65 girls) and 909 seizures were included. The demographic characteristics of the patients and seizures are presented in Table 1.

3.2. Relationship between semiologic seizure types and sleep/wake, day/night states, and 3-h time intervals

In total, 568 (62.5%) seizures occurred in wakefulness and 341 (37.5%) seizures occurred in sleep. Auras, dialeptic, myoclonic, and hypomotor seizures and epileptic spasms occurred more frequently in wakefulness, whereas tonic, clonic, and hypermotor seizures occurred more often in sleep. All atonic seizures occurred during wakefulness. We analyzed only one gelastic seizure that was seen in wakefulness. No difference was noticed between versive, tonic-clonic, and automotor seizures in wakefulness or in sleep. The results and significance levels are presented in Table 2.

A total of 509 (56%) seizures occurred during daytime and 400 (44%) seizures occurred at night. Auras, dialeptic, atonic seizures, and epileptic spasms occurred more often during daytime. Hypermotor seizures occurred more frequently at night. There was no difference between the daytime or nighttime distribution of tonic, clonic, versive, tonic-clonic, automotor, myoclonic, and hypomotor seizures. The results and significance levels are presented in Table 2.

When we considered the circadian patterns of semiologic seizure types using a 3-h time interval, irrespective of sleep/wake status, distributions of auras ($p < 0.001$), hypermotor ($p < 0.01$), myoclonic ($p < 0.01$), tonic ($p < 0.01$), atonic seizures ($p < 0.05$), and epileptic spasms ($p < 0.01$) were significant. The results are presented in Fig. 1.

Table 1 – Descriptive data of patients and seizures.

Characteristics	Values
Patients	
Total patients	170
Girls/boys, n (%)	105/65 (61.8/38.2)
Mean age, years (SD)	11.4 (4.1)
Onset of seizures, years (SD)	5.2 (4.1)
Mean duration of monitoring, days (SD)	3.6 (1.5)
Average seizures/patient, *n* (SD)	5.3 (3.4)
Mean AEDs/patient, *n* (SD)	2.5 (1.1)
No AED, *n* (%)	6 (3.5)
One AED, *n* (%)	27 (15.9)
Two AEDs, *n* (%)	75 (44.1)
Three AEDs, *n* (%)	47 (27.6)
Four or more AEDs, *n* (%)	15 (8.9)
Cause	
İdiopathic, *n* (%)	3 (1.8)
Symptomatic, *n* (%)	78 (45.9)
Cryptogenic, *n* (%)	89 (52.4)
Seizure localization (n = 170 patients/n = 909 seizures)	
Generalized	34/234
Temporal	37/163
Frontal	23/123
Occipital	9/52
Parietal	3/20
Multilobar	64/317
Seizures	
Semiology (n = 909)	
Aura, *n* (%)	215 (23.7)
Tonic	183 (20.1)
Dialeptic	127 (14.0)
Epileptic spasm	67 (7.4)
Clonic	57 (6.3)
Myoclonic	50 (5.5)
Hypermotor	48 (5.3)
Hypomotor	47 (5.2)
Automotor	31 (3.4)
Versive	29 (3.2)
Atonic	45 (5.0)
Tonic-clonic	9 (1.0)
Gelastic	1 (0.1)

3.3. Relationship between seizure localization and sleep/wake, day/night states, and 3-h time intervals

Generalized, occipital, and multilobar seizures were seen mostly during daytime and in wakefulness. Frontal lobe seizures occurred more often at night and in sleep. Temporal seizures occurred more frequently in wakefulness and parietal seizures were seen mostly during daytime. The results and significance levels are presented in Table 2.

When we considered the circadian patterns of seizure localization using a 3-h time interval, irrespective of sleep/wake status, generalized seizures more commonly seen between 12:00 and 18:00 h, and frontal lobe seizures between 24:00 and 3:00 h. The distributions of temporal and occipital seizures showed 2 peaks; temporal lobe seizures peaked at the 06:00–09:00 h and 12:00–15:00 h time intervals; occipital lobe seizures peaked at the 09:00–12:00 and 15:00–18:00 h time intervals. There was no significant distribution of multilobar and parietal lobe seizures during the 3-h time intervals. The results are presented in Fig. 2.

4. Discussion

In this study, we report the circadian distribution of seizures according to seizure semiologic subtypes and seizure onset localization in children who were referred to our tertiary epilepsy center for video-EEG monitoring. Semiology and seizure location were found to be determinants of the circadian distribution of seizure occurrence.

4.1. Sleep/wake, day/night state, and circadian patterns of different semiologic seizure types

In the literature, studies on the circadian distribution of semiologic seizure types are limited. Loddenkemper et al.[11] described 225 children (1008 seizures) and found that auras, dialeptic, atonic, myoclonic, and hypomotor seizures and epileptic spasms occurred more frequently in wakefulness,

Table 2 – Seizure semiologic subtypes, localization, and occurrence of seizures during wakefulness/sleep and daytime/night states.

Seizure semiology, location	Wakefulness	Sleep	P	Daytime	Night	P
A. Semiologic seizure types and wake/sleep, day/night states						
Aura	185	30	<0.001	143	72	<0.001
Dialeptic	84	43	<0.001	78	49	<0.05
Tonic	56	127	<0.001	84	99	NS
Clonic	14	43	<0.001	22	35	NS
Versive	18	11	NS	16	13	NS
Tonic-clonic	4	5	NS	4	5	NS
Automotor	12	19	NS	16	15	NS
Hypermotor	8	40	<0.001	16	32	<0.05
Myoclonic	46	4	<0.01	25	25	NS
Hypomotor	34	13	<0.01	26	21	NS
Atonic	45	0	–[a]	37	8	<0.001
Epileptic spasm	61	6	<0.001	41	26	<0.05
Gelastic	1	0	–[a]	1	0	–[a]
B. Location of seizures and wake/sleep, day/night states						
Generalized	189	45	<0.001	142	92	<0.001
Temporal	100	63	<0.05	88	75	NS
Frontal	44	79	<0.001	41	82	<0.001
Occipital	45	7	<0.001	39	13	<0.001
Parietal	12	8	NS	15	5	<0.05
Multilobar	178	139	<0.05	184	133	<0.05

NS, not significant.
[a] The "0" in these categories limit statistical analysis.

whereas tonic and hypermotor seizures occurred more often in sleep. Our results are in agreement with these findings except for the sleep/wake patterns of clonic, tonic-clonic, and automotor seizures. This may be due to the low number of seizures in these groups in our series. When we look at the day–night pattern of semiologic seizure subtypes in Loddenkemper et al.'s study,[11] only the distribution of hypermotor and atonic seizures is compatible with our findings.

In the study of Ramgopal et al.,[12] epileptic spasms occurred predominantly during wakefulness and in daytime. Zarowski et al.[13] analyzed the chronobiology of only generalized seizures and found that atonic seizures, myoclonic seizures, and epileptic spasms occurred more often during wakefulness and atonic seizures occurred more frequently during daytime, as was shown in our study.

Hofstra et al.[14] studied both adults and children and observed that partial tonic seizures peaked in the early morning hours. Loddenkemper et al.[11] found that hypermotor seizures peaked between 24:00–09:00 h and atonic seizures peaked between 06:00–09:00 h. These results are also consisted with our data.

4.2. *Sleep/wake, day/night state, and circadian patterns of different seizure localizations*

When we evaluated the seizure occurrence according to seizure localization, generalized, occipital, and multilobar seizures were seen mostly during daytime and in wakefulness. Frontal lobe seizures occurred more often at night and in sleep. Temporal seizures occurred more frequently in

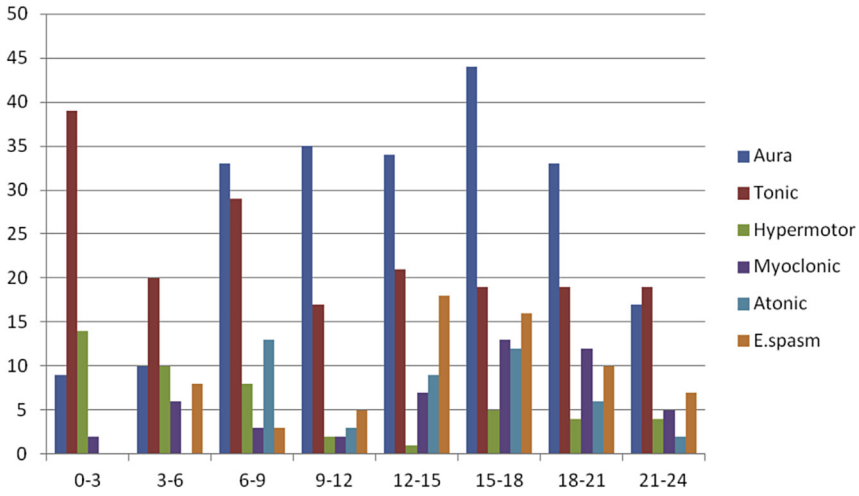


Fig. 1 – Distribution of seizure semiologic subtypes within 3-h time blocks.

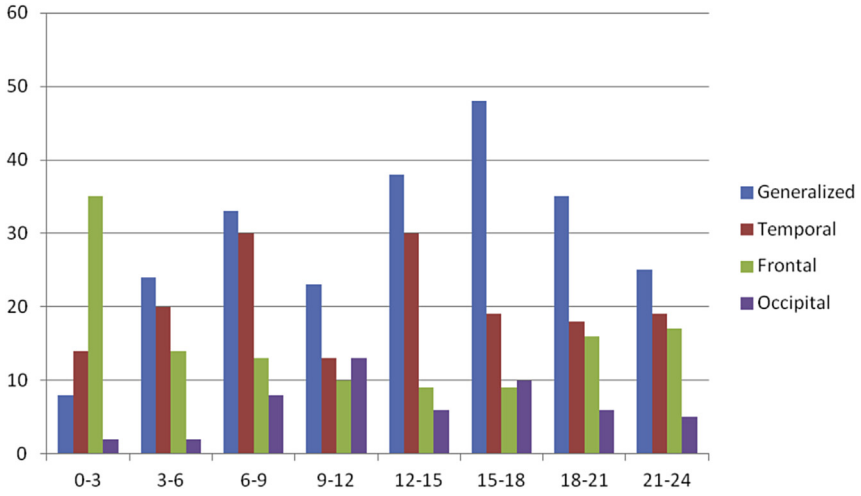


Fig. 2 – Distribution of seizures according to localization within 3-h time blocks.

wakefulness and parietal seizures were seen mostly during daytime. Our observations confirm the findings of previous studies. Bazil and Walczak[6] found that frontal lobe seizures were more likely to occur during sleep than temporal lobe seizures. Crespel et al.[7] showed that 61% of frontal lobe seizures occurred during sleep and 89% of temporal lobe seizures occurred during wakefulness in adults. One study noted that frontal lobe seizures occurred most frequently in sleep, whereas temporal lobe, especially neocortical temporal lobe seizures, and occipitoparietal lobe seizures occurred more frequently in wakefulness.[8]

Studies on the daily distribution of temporal lobe seizures are relatively common. In one case study based on a seizure diary maintained for 5 years, the peak incidence of temporal seizures was found at 12:10 h.[15] In another study including 98 adult patients (1350 seizures), the pattern of partial seizure occurrence in adults was compared with that of seizures in an epileptic rat model. It was found that mesial temporal lobe seizures peaked at 15:00 h.[4] Hofstra et al.[14] described 76 children (396 seizures) and 100 adult patients (412 seizures) and found that, in children, temporal lobe seizures occurred most frequently in the time bins of 05:00–11:00 h and 11:00–17:00 h. Hofstra et al.[16] also studied the distribution of seizures using intracranial EEG monitoring. In this study, 26 adults and 7 children were analyzed. They found that mesial and neocortical temporal lobe seizures peaked at 11:00–17:00 h. Our results also confirm these studies. Pavlova et al.[17] found a significant peak in the 15:00–19:00 h time bin for temporal lobe seizures and a peak in the 19:00–23:00 h bin in the extratemporal lobe epilepsy patients. These peak hours do not correlate with our results.

Bimodal distribution of temporal lobe seizures was seen in some studies. Durazzo et al.[18] evaluated 131 adult patients (669 seizures) with intracranial EEG recordings and found that mesial temporal lobe seizures were bimodally distributed with a primary peak occurring in the late afternoon between 16:00 and 19:00 h and a secondary peak occurring in the morning between 7:00 and 10:00 h. In this study, neocortical temporal seizures peaked between 13:00 and 16:00 h.[18] Similarly, in another study of adult patients with mesial temporal lobe seizures, a bimodal pattern of seizure occurrence was found between 06:00 and 08:00 h and between 15:00 and 17:00 h.[19] In our study, we also found a bimodal distribution of temporal lobe seizures, but the peak in the afternoon (12:00–15:00 h) was a little earlier. This shift may be related to the inclusion of both mesial and neocortical temporal lobe seizures in our study.

Our findings support studies that have shown that frontal lobe seizures peaked in the early morning hours.[11,16,18]

Data on the circadian pattern of the occipital and parietal lobes are very limited. In one study including adult patients, occipital lobe seizures peaked between 16:00 and 19:00 h and in another study including children, the peaks for occipital lobe seizures were consistent with the peaks observed in our study.[11,18] Our findings on the sleep/wake circadian pattern of parietal lobe seizures are not in agreement with the results in the literature. In those studies, parietal lobe seizures peaked at night and in sleep.[11,15,18] This conflict may be due to the insufficient number of parietal lobe seizures in our study.

In some studies,[11,13] generalized seizures frequently occurred during wakefulness, in daytime and this is in agreement with our findings. In our study, generalized seizures peaked between 12:00 and 18:00 h. But Loddenkemper et al.[11] found that generalized seizures occurred more frequently between 06:00 and 12:00 h. In one study,[20] an increase in cortical excitability in the early morning in patients with idiopathic generalized epilepsy was reported. The difference in the peak time of generalized seizures may be due to the lack of patients with idiopathic generalized epilepsy in our series.

It is obvious that the occurrence of epileptic seizures follow a circadian pattern depending on seizure semiology and location. But the underlying mechanisms remain unclear. A connection with the master circadian pacemaker that is formed by the cells of the suprachiasmatic nuclei (SCN) has been postulated.[21,22] The SCN, located in the anterior hypothalamus, has connections with the pineal gland, thalamus, hypothalamus, and the limbic system in the brain. In this way, the SCN is related to the centers that play important roles in the epileptic network. This may explain the specific circadian patterns of excitability and susceptibility for different seizure types and localizations in epilepsy patients.[22]

4.3. *Limitations*

There are some limitations that should be taken into account when interpreting our results. The data in this study were collected from a tertiary center. The patients in this study were admitted to our center especially for intractable epilepsy and presurgical evaluation. For this reason, this study does not reflect the average epilepsy population. Patients were permitted to sleep and wake at their own discretion; however, routine inpatient activities such as physician rounds, nursing care, and meal times and exposure to light, noise, and other sleep disturbances in hospital may have an influence on the circadian rhythms of the patients. In addition, tapering antiepileptic medication may also change the frequency and timing of seizures.

We use superficial EEG monitoring. Scalp EEG has limitations in the detection of seizure onset localization. Also we did not have additional electromyography and electrooculography electrodes, so we could not identify the sleep stage. Seizures were included when we observed clinical symptoms with simultaneous ictal activity on EEG. Subclinical seizures were excluded. So we may have missed very subtle clinical seizures.

In our study, wakefulness or sleep were assessed regardless of the time of the day. Daytime sleep or night sleep were not analyzed separately. This could be a confounding factor for the results.

5. Conclusions

This study suggests that the occurrence of seizures in children shows a circadian pattern and specific sleep/wake distribution depending on seizure semiology and location. Recognition of these daily patterns of seizures provides new diagnostic and therapeutic management options. But further studies will be required to identify the underlying mechanisms in the timing of seizures.

Conflicts of interest

None.

Acknowledgments

The authors thank Ms. Serpil Kılavuz, video-EEG technician, for her help with the video-EEG monitoring and all their colleagues for their help in the follow-up of patients.

REFERENCES

1. Gowers W. Course of epilepsy. In: Gowers W, editor. *Epilepsy and other chronic convulsive diseases: their causes, symptoms and treatment*. New York: William Wood; 1885. p. 157–64.
2. Langdon-Down M, Brain WR. Time of day in relation to convulsions in epilepsy. *Lancet* 1929;**1**:1029–32.
3. Cavalheiro EA, Leite JP, Bortolotto ZA, et al. Long-term effects of pilocarpine in rats: structural damage of the brain triggers kindling and spontaneous recurrent seizures. *Epilepsia* 1991;**132**:778–82.
4. 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.
5. Quigg M, Clayburn H, Straume M, Menaker M, Bertram 3rd EH. Effects of circadian regulation and rest-activity state on spontaneous seizures in a rat model of limbic epilepsy. *Epilepsia* 2000;**41**:502–9.
6. Bazil CW, Walczak TS. Effects of sleep and sleep stage on epileptic and nonepileptic seizure. *Epilepsia* 1997;**38**:56–62.
7. Crespel A, Baldy-Moulinier M, Coubes P. The relationship between sleep and epilepsy in frontal and temporal lobe epilepsies: practical and physiopathologic considerations. *Epilepsia* 1998;**39**:150–7.
8. Herman ST, Walczak TS, Bazil CW. Distribution of partial seizures during the sleep–wake cycle: differences by seizure onset site. *Neurology* 2001;**56**:1453–9.
9. Minecan D, Natarajan A, Marzec M, Malow B. Relationship of epileptic seizures to sleep stage and sleep depth. *Sleep* 2002;**25**:899–904.
10. Lüders H, Acharya J, Baumgartner C, et al. Semiological seizure classification. *Epilepsia* 1998;**39**:1006–13.
11. Loddenkemper T, Vendrame M, Zarowski M, et al. Circadian patterns of pediatric seizures. *Neurology* 2011;**76**:145–53.
12. Ramgopal S, Shah A, Zarowski M, et al. Diurnal and sleep/wake patterns of epileptic spasms in different age groups. *Epilepsia* 2012;**53**:1170–7.
13. Zarowski M, Loddenkemper T, Vendrame M, et al. Circadian distribution and sleep/wake patterns of generalized seizures in children. *Epilepsia* 2011;**52**:1076–83.
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. Dual epileptic foci in a single patient express distinct temporal patterns dependent on limbic versus non-limbic brain location. *Ann Neurol* 2000;**48**:117–20.
16. Hofstra WA, Spetgens WP, Leijten FS, et al. Diurnal rhythms in seizures detected by intracranial electrocorticographic monitoring: an observational study. *Epilepsy Behav* 2009;**14**:617–21.
17. Pavlova MK, Shea SA, Bromfield EB. Day/night patterns of focal seizures. *Epilepsy Behav* 2004;**5**:44–9.
18. Durazzo TS, Spencer SS, Duckrow RB, et al. Temporal distributions of seizure occurrence from various epileptogenic regions. *Neurology* 2008;**70**:1265–71.
19. Karafin M, St Louis EK, Zimmerman MB, Sparks JD, Granner MA. Bimodal ultradian seizure periodicity in human mesial temporal lobe epilepsy. *Seizure* 2010;**19**:347–51.
20. Badawy RA, Macdonell RA, Jackson GD, Berkovic SF. Why do seizures in generalized epilepsy often occur in the morning? *Neurology* 2009;**73**:218–22.
21. Hofstra WA, de Weerd AW. The circadian rhythm and its interaction with human epilepsy: a review of literature. *Sleep Med Rev* 2009;**13**:413–20.
22. 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.