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IS THERE A CIRCADIAN VARIATION OF EPILEPTIFORM ABNORMALITIES IN IDIOPATHIC GENERALIZED EPILEPSY?

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Abstract

Epileptiform abnormalities often occur at specific times of day or night, possibly attributable to state of consciousness (sleep vs. wake) and/or influences from the endogenous circadian pacemaker. In this pilot study we tested for the existence of circadian variation of interictal epileptiform discharges (IED), independent of changes in state, environment, or behavior. Five patients with generalized epilepsy underwent a protocol whereby their sleep/wake schedule was evenly distributed across the circadian cycle while undergoing full montage electroencephalography and hourly plasma melatonin measurements. Light was <8 lux to prevent circadian entrainment. All patients completed the protocol testifying to its feasibility. All patients had normal circadian rhythmicity of plasma melatonin relative to their habitual sleep times. In the three patients with sufficient IED to assess variability, most IED occurred during NREM (ratio NREM: Wake = 14:1; $P < 0.001$). In both patients who had NREM at all circadian phases, there was apparent circadian variation in IED but with different phases relative to peak melatonin.

Keywords

circadian; epilepsy; idiopathic generalized epilepsy; sleep; nocturnal; interictal discharges; sleep/wake distribution

Introduction

Although epilepsy is a chronic condition, individual seizures occur at discrete times, which may not be random. A 24-hour periodicity in the times when seizures occur has been described and appears to vary by epilepsy syndrome, as well as among different epileptogenic regions [1;2;3]. Well described clinical examples include generalized tonic-clonic seizures on awakening and morning myoclonus in juvenile myoclonic epilepsy. When an event occurs systematically or preferentially at a specific time, an obvious cause to examine is the state of consciousness: sleep vs. wakefulness. However, the endogenous circadian system (or a specific circadian phase) may be an independent or contributing cause of these events.

In idiopathic generalized epilepsy (IGE), day/night patterns of ictal and interictal discharges have received relatively little attention, but Kellaway et al. [9] found that generalized spike-

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wave discharges were much more likely to occur during sleep. More studies have been performed in patients with localization-related epilepsy. In these patients there is also a well reported effect of sleep/wake state on the occurrence of seizures, as well as of interictal discharges [4; 5; 6; 7; 8]. Both ictal and interictal discharges have a strong tendency to occur in NREM sleep, while few interictal discharges and very few seizures occur in REM [4;5].

Many normal physiologic functions have endogenous circadian periodicity, i.e., daily rhythms that persist under constant behavioral and environmental conditions that are regulated by the master circadian pacemaker located in the suprachiasmatic nucleus. Well-established examples include the rhythms of plasma cortisol and melatonin, urine volume and body temperature, which retain their variation according to circadian phase, even when an individual is continuously awake (state of consciousness is constant). In some physiological functions, sleep/wake state and circadian phase both have strong and independent effects and the result can be seen as an interaction of these two processes. For example, plasma levels of thyroid stimulating hormone (TSH) are usually higher during the 'biological night' if an individual remains awake, but TSH is suppressed by sleep itself, such that when an individual is asleep at night the circadian-driven increase is blunted [10].

An endogenous circadian influence on epileptiform activity has been seen in an rat model of limbic epilepsy, that of electrically induced status epilepticus [11]. Using this animal model, studied throughout a rigorous circadian protocol, Qugg et al. found that epileptiform activity occurs at the same circadian time, regardless of whether the rats were awake or asleep. In humans with temporal lobe epilepsy, retrospective analyses revealed a robust increase in the number of seizures in the mid-afternoon[1; 3], suggesting that factors independent of the state of sleep or wakefulness may affect the timing of seizures. However, these human studies were performed under clinical diagnostic conditions and factors other than the endogenous circadian rhythm may have lead to the observed variations.

To establish the true **circadian** nature of a physiologic or pathophysiologic function, it is necessary to separate the effects of the endogenous circadian system from those of behavioral and environmental effects. One technique that enables this separation in humans is termed a 'forced desynchrony' protocol (FD), during which all behaviors are evenly scheduled across all phases of the circadian cycle, while maintaining environmental influences (light, temperature, etc.) constant. This is achieved by imposing a recurring artificial 'day' length that is outside the range of entrainment of the internal circadian pacemaker, while having subjects live under dim light conditions. The length of these laboratory 'days' has been varied from 20 minutes to 42 hours, usually with one-third of the period allotted as sleep opportunity. The longer the 'day' length, the longer the protocol must be in order to distribute all sleep/wake behaviors evenly across the circadian cycle. For example, if the laboratory 'day' is 28 hours, the protocol takes one week to complete. The FD is usually an intense and long laboratory protocol requiring exceedingly cooperative subjects with sufficient free time to volunteer. To find such subjects in a particular patient population is difficult. Thus, we designed the current protocol with a short 'day' length (5 hours and 40 minutes) to test the feasibility of completing an FD protocol within 3 days, which would help optimize recruitment and study completion in epilepsy patients.

Studying seizures in conditions that allow true separation of circadian, and behavioral plus environmental influences is complicated for a number of reasons. For instance, there is the potential need for intervention at the time a seizure occurs, and seizures themselves may potentially influence biological markers of circadian phase (e.g., body temperature or hormones measured), and any gross body movements during seizures could also compromise the recordings themselves. On the other hand, examining any circadian variation in the occurrence of interictal epileptiform discharges (IED) in patients with

idiopathic generalized epilepsy is an attractive alternative. In this group (as opposed to focal epilepsy), the timing of IED is of likely clinical significance because IED are morphologically similar to the ictal discharges typically associated with absence seizures in patients with IGE [12], and because bursts of spike-wave discharges, especially those longer than 3 seconds, may be associated with transient cognitive impairment [13;14]. Furthermore, there is a potential nocturnal predominance the IEDs in patients with IGE, with IEDs being much more likely to occur during sleep (and therefore at night) [9]. Thus, it is important to evaluate whether this nocturnal predominance is due to environmental conditions or behavioral state (sleep vs. wakefulness) or to an independent effect of the endogenous circadian system.

In this pilot study we aimed to test the feasibility of performing a FD protocol in patients with epilepsy. The secondary aims were to test in these patients with IGE: (a) whether or not there exists an endogenous circadian variation of IED and (b) to establish whether the circadian phase and amplitude of plasma melatonin profiles are normal in these patients.

Methods

This was a prospective pilot study of individuals with IGE. The protocol was approved by the Institutional Review Board of Brigham and Women's Hospital/Partners Health Care.

Subjects

Patients were recruited from neurology clinics and by advertisements on internet sources and local newspapers. After a screening telephone interview, the interested patients had a physical exam and interview with the study physician, followed by screening laboratory tests, electroencephalography (EEG, if none was available), psychology interview (to assess risk for psychiatric disturbance during the study), and polysomnogram (to rule out major sleep abnormalities). We included patients with IGE, diagnosed on the basis of clinical history, EEG showing generalized spike-wave discharges, and normal brain MRI. Our specific inclusion/exclusion criteria were as follows:

Inclusion Criteria—1) Diagnosis of or generalized epilepsy with supporting evidence from EEG, imaging and medical history data; 2) Age 18–65; 3) Medical condition. Volunteers had to be ambulatory and have no major visual or auditory handicaps. Medical suitability was determined by clinical history, physical examination, chemistry and hematology screening assay, 12 lead electrocardiogram, and, where appropriate, medical records as obtained after subject consent; 4) Usual frequency of simple partial, myoclonic or absence seizures less than 20/month (by history of the last 2 months); 5) Unchanged seizure frequency and medication treatment for at least to months.

Exclusion criteria—1) Prior hospitalization for status epilepticus; 2) Generalized seizure within the previous eight weeks; 3) Active or recent (within the past 3 years) verified substance abuse; 4) Other active untreated medical conditions (such as cardiac, pulmonary, severe gastrointestinal, neurological [except epilepsy], or psychiatric disorders); 5) Transitions from time zones (>2 hour) or shift work within the past 3 months; 6) Narcolepsy, moderate or severe sleep apnea, or parasomnia (from screening polysomnogram); 7) Affective disorders (bipolar disorder or seasonal affective disorder); 8) History of circadian rhythm disturbance (advanced or delayed sleep phase syndrome); 9) Major visual handicap (since it may affect circadian rhythms); 10) Psychological disturbances (since it may be risky for an individual to participate in circadian rhythm studies).

Protocol

Ambulatory baseline—Each subject had to maintain a regular, self-selected sleep-wake schedule for at least 2 weeks before entry into the laboratory, verified by a sleep diary and wrist actigraphy (Actiwatch-L). During this segment, major events such as medication changes and seizure-provoking factors were recorded in a diary.

Forced desynchrony – in laboratory—Each subject stayed in an individual laboratory suite in constant environmental conditions including dim light (below 8 lux) to prevent circadian entrainment. No external time cues were available. Following a habituation night, patients underwent an FD protocol whereby the sleep/wake schedule was evenly distributed across the circadian cycle by scheduling 11 recurring periods of 5 hours and 20 min with equal time devoted to scheduled wakefulness and sleep opportunity within each period (Fig 1). We provided equal time for sleep opportunity and wakefulness to avoid any accruing sleep deprivation during the FD, which could conceivably affect IED frequency. After this FD protocol was completed, the patients were allowed to sleep ad lib. overnight, to further ensure that they were not sleep deprived upon discharge (recovery period).

Measurements

EEG was recorded throughout the laboratory stay using anterior temporal as well as standard 10–20 EEG electrodes. EMG and EOG leads were added to aid with sleep stage scoring. We used the EEG data to assess sleep-wake states and IED. Hourly blood samples from indwelling catheter were collected for plasma melatonin assays via radioimmunoassay I¹²⁵ (Pharmasan Laboratories, Osceola, WI, USA). The sensitivity of the melatonin assay was 0.7 pg/mL, and the inter-assay coefficients of variation were 13.2% and 8.4% at mean concentrations of 17.3 and 69 pg/mL, respectively.

Continuous pulse oximetry, ECG, and daily hematocrit and platelets were monitored as additional safety measures.

Analyses

Analysis of discharges—The recording were screened visually for IED (spikes and rhythmic spike-wave bursts) by two trained epileptologists (MKP and EBB), both blinded to data acquisition time. IED were counted as one discharge (or one event) regardless of whether they consisted of a single spike-wave complex or a burst of several spike-wave complexes. In any instances of doubt on whether a discharge should be included or not, both reviewers met and reviewed the records. Only IEDs for which both reviewers agreed upon were included in the analysis.

Sleep scoring—For all patients who had a meaningful number of discharges, sleep was staged as REM, N1, N2, N3, according to current scoring criteria by an independent polysomnographic trained technician who was also blinded to time.

Circadian phase marker—Circadian phases (0°–359°) were assigned to all data based on the circadian rhythmicity of plasma melatonin, as computed by a nonorthogonal spectral analysis technique with two harmonics [15]. The fitted melatonin maximum was assigned 0°. Dim light melatonin onset (DLMO_{25%}) was calculated as the interpolated time point when melatonin levels exceeded 25% of the fitted peak [16].

The number of IEDs per minute was assigned to state of consciousness (Wake, NREM [grouping N1, N2, N3], or REM) and to 60-degree circadian bins (0° bin encompassed the phase window from 330° to 30°, etc.). Each 60° circadian bin corresponds to four hours of clock time.

Statistical analysis—The frequency of IED during Wake vs. NREM and across the circadian cycle was analyzed by Mixed Model analysis of variance with patients as random factor and state (Wake, NREM) and circadian bin (6 bins) as fixed factors.

Results

Protocol feasibility

We screened eight patients with generalized epilepsy and enrolled five in the FD protocol, four with juvenile myoclonic epilepsy (JME), and one with idiopathic generalized epilepsy, unspecified (probably either JME or generalized tonic-clonic seizures upon awakening). Detailed clinical data on each subject are presented in Table 1. Age ranged from 18 to 28 years (three women and two men). Reasons for not starting the protocol in three screened patients included change of availability in two and moderate sleep apnea in one. All patients who started the laboratory protocol completed the protocol, and without any adverse events. No patients experienced seizures during the protocol.

Three of the patients had sufficient IED in both wakefulness and sleep in order to examine circadian and behavioral factors. The fourth subject had only two discharges (both during sleep during the biological night) and the fifth had no discharges at all.

Normal circadian melatonin pattern in patients with generalized epilepsy

In all 5 patients, plasma melatonin concentration followed the well established circadian pattern described in healthy subjects, including normal timing relative to sleep, normal duration between consecutive peaks, and normal amplitude.

The DLMO_{25%} had consistent timing among the patients relative to their habitual sleep time. DLMO_{25%} occurred 1 h 47 min $\pm$ 1 h 30 min (mean $\pm$ SD) prior to habitual bedtime (range from 4 h 12 min to 40 min prior to habitual bedtime). This is consistent with values obtained for similarly aged healthy subjects in the same laboratory (n = 32, mean 2 h 9 min $\pm$ 1 h 2 min prior to habitual bedtime; range from 4 h 28 min prior to habitual bedtime to 33 min after habitual bedtime; [17]).

The average time of the second DLMO_{25%} in the protocol was 24 h 19 min after the first DLMO_{25%} (range among patients 23 h 48 min to 24 h 43 min). This difference between consecutive DLMO_{25%} collected under dim light conditions in this patient group is similar to the mean human circadian period of healthy subjects studied in the same laboratory (mean 24 h 18 min; [15]).

The curve-fitted maximum of the melatonin profile also showed very consistent timing among our patients relative to their habitual sleep time. Melatonin maximum occurred 2.65 $\pm$ 0.29 h (mean $\pm$ SD) following habitual bedtime. Thus, a 0⁰ phase in these 5 individuals would correspond to clock time ranging from 02:11 to 05:22.

The profile of melatonin is similar in all 5 patients with a sharp increase, followed by a plateau and a sharp decrease at the end of the ‘biological night’ (Fig. 2). This profile is similar to the profiles typically found in healthy individuals during other FD protocols with longer laboratory day lengths [14]. However, one unusual feature in most of these patterns is a mild to moderate brief ‘dip’ in plasma melatonin close to the midpoint of melatonin secretion. This decrease is likely due to the change in body position from standing to lying down that occurred every 5 hours 20 minutes [16]. Despite the presence of such dips, the average fitted peak-to-trough amplitude of plasma melatonin was 78.2 $\pm$ 20.0 pg/mL with range 61.8–112.8 pg/mL (336 $\pm$ 85.9 pmol/L; 266–485 pmol/L), which is consistent with values obtained for similarly aged healthy subjects in the same laboratory [17].

Sleep/wake distribution

The mean percentage of wakefulness, REM, and NREM is presented in Fig. 3 (lowest panel) for the 3 patients who had sufficient epileptiform discharges throughout the FD such that temporal variability could be assessed. Sleep was observed during all sleep opportunities in two of these patients and in all but one sleep opportunity in the other subject. As scheduled, wakefulness occurred in all circadian phases. The total proportion of sleep across the FD protocol averaged 35%, ranging from 31–38% among subjects. REM sleep comprised an average of 20% of all sleep, ranging from 18 to 22% among subjects. Hence, sleep deprivation was avoided and the overall distribution of NREM and REM appeared relatively normal throughout for each subject. Across circadian phase, the proportion of NREM sleep ranged from 15–37% (including the 50% period of scheduled wakefulness), and the proportion of REM sleep ranged from 1–18% (Figure 3).

Circadian and sleep vs. wake distribution of IED

Of the three patients with sufficient IED to examine circadian influences, the number of IED during the FD varied from 88 to 7661. Few IEDs occurred in REM sleep, thus the analysis was segregated into wakefulness and NREM sleep. There were systematically more IED during NREM sleep as compared to wake independent of the circadian cycle (mean discharges in wake = 29.4; mean NREM sleep = 412.7; $P=0.0004$). The ratio of discharges in NREM to wakefulness was 14:1.

The variation in the frequency of discharges according to circadian phases is presented for each subject in Figure 3. In the first and third patients there appeared to be clear circadian rhythms of IED in NREM sleep, although the timing of peaks and troughs were different between these two patients. In the other subject there also appeared to be an underlying rhythm of IED in NREM sleep that was similar in phase as occurred in the third subject although the rhythm could not be reliably assessed due to a lack of sleep in one circadian bin. When considered on the same absolute scale, any circadian rhythms in IED during wakefulness appeared less impressive (Figure 3). Nonetheless, the highest frequency of IED occurred in the same circadian phase during NREM and wakefulness in subject one (both peaked in phase bin centered around 300°, spanning the approximate clock time period of 23:22–03:22 h) and in subject two (both peaked in phase bin centered around 180°, spanning the approximate clock time period of 15:40–19:40 h). Moreover, when IED variation during wakefulness is considered on a relative scale, there was a many-fold increase in the frequency of IED at these specific phases, suggesting that individual circadian rhythmicity may occur in both wakefulness and NREM sleep, albeit at different mean frequencies.

For the group ANOVA, since the phases of any rhythms were inconsistent among patients, a circadian variation in IED did not reach significance. In addition, we found no significant interaction between circadian bin and sleep/wake state (NREM vs. Wake).

Discussion

This is the first study to use a rigorous circadian protocol in humans with epilepsy. We have four main findings: 1) the protocol used is feasible and likely safe in patients with generalized epilepsy; 2) the overall profile of melatonin in these patients in the absence of seizures is similar to the ones previously reported in healthy individuals; 3) there was a 14-fold higher number of discharges in sleep as compared to wakefulness - independent from any circadian effects; 4) there was a suggestion of a circadian variation in discharges-independent from any sleep/wake effects, but it was different among subjects.

This short FD protocol is clearly feasible in patients with epilepsy. In particular: (a) The duration of the overall laboratory protocol was short enough to allow recruitment from a

very limited patient population; (b) There were normal overall proportions of NREM, REM and wakefulness, and without accruing sleep deprivation (sleep averaged 35%, a similar ratio to the normal 8 hours sleep across a 24 hour period); (c) we were able to assess the independent effects of circadian and sleep/wake influences upon the frequency of IED under constant environmental conditions; (d) the short sleep-wake intervals allowed patients to keep their medication schedule essentially unchanged when in the laboratory; and (e) the protocol appeared tolerable and did not induce any adverse events.

The selection of a reliable circadian phase marker in individuals with epilepsy was a significant concern. Seizures, as well as focal epilepsy in itself, tend to affect the pulsatile pituitary secretion. For example, during interictal periods in men with temporal lobe epilepsy it was found that luteinizing hormone has a lower mean concentration, slower pulsing rate, and higher peak amplitude when compared to those parameters in healthy control subjects [19]. Additionally, the secretion of luteinizing hormone may be significantly altered by seizures [20]. Regarding pineal function, a brief report on patients with localization-related epilepsy in hospital conditions (i.e., a protocol that could not fully control for the levels of light, which strongly suppresses melatonin) [21] suggested that melatonin may be relatively low in epilepsy patients, and could be affected by seizures. However, in our study, under controlled dim light conditions and without the occurrence of clinical seizures, plasma melatonin appeared as a robust circadian phase marker in IGE patients (Fig. 2), despite an adjusted sleep/wake schedule (Fig. 1), the presence of varied frequencies of IEDs (Fig. 3) and various anti-epilepsy medications (Table 1). The melatonin retained a circadian profile that was quite similar to that of healthy individuals [22] (apart from a small dip, likely due to postural effects). The similarity of melatonin results in these patients and healthy controls in terms of melatonin phase angle (DLMO relative to habitual sleep time [18], and melatonin peak [22; 17], suggests that melatonin is a useful circadian phase marker in IGE patients.

We found a 14-fold increase in the number of IED in NREM sleep, as compared to wakefulness - independent from any circadian effects. Prior reports indicate that the state of consciousness influences the frequency of IED [9], but also affects the morphology of the IED. In comparison with the classic 3 Hz generalized spike-wave bursts of typical absences in wakefulness, during sleep, these bursts tend to be shorter (often isolated), slower (<3 Hz), and more likely to include polyspike-waves than those recorded during wakefulness [23]. Due to the small number of patients, which limits interpretation of any comparisons, we focused on the frequency, rather than the morphology of the discharges. In this respect, our finding is consistent with prior observations of a sleep/wake distribution of IED in patients with IGE.

We found some evidence of individual circadian effects on the frequency of IED, independent of the sleep/wake state, although these influences were not statistically significant in the group average data, likely due to differences in phases among subjects. Previously, Kellaway et al [9] observed that the variation in the frequency of IID over time often had a bimodal daily pattern (in 9/19 subjects) with the first peak occurring early in the night and the second at the end of the night and usually persisting into morning awakening. The former night peak may be due to the aforementioned increase during NREM sleep, which is most prevalent during the first part of the night (with increasing amount of REM sleep at the end of the night). The latter night peak may be of particular clinical importance because in several IGE syndromes, particularly those arising during adolescence, seizures tend to occur within an hour or two after awakening [24]. These syndromes were only beginning to be recognized in the 1980's, and Kellaway et al [9] do not present the ages of epilepsy onset in their patients. Although Kellaway et al [9] were unable to assess whether such peaks were due to underlying circadian rhythms and/or behavioral effects, we did not

find a systematic increase in IED during the biological night in our patients (Fig. 3, phase bins 300° and 0°, or the bins around 11:00 p.m. – 3:00 a.m.), suggesting that the nocturnal predominance of IED in Kellaway et al.'s study is due to a primary effect of NREM sleep rather than circadian rhythmicity. Alternatively, we can speculate that the IED peak at the end of the biological night in two of our patients (Fig. 3, patients 2 and 3, phase bins 60°, corresponding to the interval around 7:00 – 11:00 a.m.) and the one seen at the beginning of the biological night in the other subject (Fig. 3, patient 1, phase bin 300° or between 10:10 p.m. and 2:10 a.m.), could correspond to the bimodal peaks noted in many subjects by Kellaway et al. This hypothesis is particularly attractive in that all of our patients had adolescent-onset IGE syndromes (with age 8 earlier than average [24]) typically characterized by seizures after waking, though this particular pattern was not always verified by the history. Thus, this area deserves further study in a larger group of patients.

Both the circadian distribution and the sleep/wake distribution of the discharges in our IGE patients differ substantially from the ones reported in studies performed in patients with localization related epilepsy. Prior studies report more seizures arising from wakefulness and seen in the mid-afternoon in patients with temporal lobe epilepsy [1;3], while patients with IGE have more seizures at night and/or during sleep[9]. This difference in the distribution of epileptiform abnormalities per state and circadian phase may in part reflect the difference in pathophysiological mechanisms. Thus, our findings are consistent with prior observations and extend these observations by use of a rigorous circadian protocol.

There are a number of limitations of our pilot study. The greatest limitation is the small number of patients which did not permit much statistical inference except concerning the robust effect of sleep/wake state in IED frequency. Other limitations include: (a) The short duration of the sleep opportunities in the FD protocol (2 h 40 min) does not allow us to examine the effect of time into sleep upon IED; (b) Since we 'binned' data obtained over at least two consecutive circadian cycles, this relies on the assumption that each IED is an independent event, and that there are no systematic changes across the protocol itself. These assumptions remain to be tested formally. Indeed, it may also be informative to perform additional analyses, such as separating IED bursts from individual spikes, and to stratify IED bursts by length; (c) For safety reasons we could not completely eliminate the effect of any antiepileptic medications. However, medications were unlikely to generate any underlying circadian variability in IED as most subjects took their medications evenly spaced across the day (Table 1).

A larger study, with comparisons between patients with localization-related and generalized epilepsies will be needed to better understand the effects of circadian rhythms in individuals with epilepsy. Based on our findings, we believe that such a study is feasible and likely to yield helpful results.

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Fig. 1. The laboratory protocol

The graph below provides visual description of our Forced Desynchrony protocol. Each horizontal line represents a 24 hour period of the laboratory stay. The white boxes represent wakefulness, and the shaded areas represent sleep opportunities. The protocol was performed in dim light (<8 lux) so that the internal circadian pacemaker continued at its inherent rate of ~ 24 hours. In that way, the protocol allows for wakefulness and sleep to be seen at all times of the circadian cycle.

Fig. 2. Melatonin profile from the ~48 hour FD protocol

The hourly plasma levels of melatonin of each of the five patient are displayed as single lines as per legend. As seen, the profile is similar in all 5 patients with a sharp increase, followed by a plateau and a sharp decrease at the end of the 'biological night'. There is a mild to moderate brief 'dip' in plasma melatonin close to the midpoint of melatonin secretion in some of the patients, likely caused by postural changes (see text). The profile is aligned according to circadian phase (presented on the x-axis). The top label presents the averaged corresponding clock times.

Fig. 3. Circadian distribution of epileptiform discharges per patient and sleep/wakefulness
Top three panels: Variation of IED across circadian phase, separately for NREM and wakefulness in three individual patients. 0 degrees represents the circadian phase of the fitted melatonin peak, which occurs around the middle of each subject's habitual sleep time. Data are double plotted (data on the left are repeated on the right) to aid visual assessment of any underlying circadian rhythmicity. The rate of IED per minute of each state (NREM, wakefulness) is averaged for each circadian bin and presented as a separate line. Underlying circadian rhythmicity is apparent particularly in NREM sleep for patients 1 and 3, as discussed in the text. As seen, the number of IED per minute in NREM is much higher than

in wakefulness in all circadian bins in patients 1 and 2, and in 5 of 6 bins in patient 3. The top label presents the corresponding clock times.

Bottom panel: Double plot of the distribution of wakefulness, NREM sleep and REM sleep in each circadian phase bin aligned according to phase of the melatonin rhythm (0 degrees represents the circadian phase of the fitted melatonin peak). In each circadian phase bin, the opportunity for sleep is 50% of the time (dashed line). The amount of sleep averaged 35% overall (equivalent to 70% of the sleep opportunity), and NREM was present at all circadian phases. The proportion of REM sleep follows an expected circadian pattern being largest at 60 degrees (for most people corresponding to the latter part of the habitual sleep period and early morning).

Table 1

Clinical data of IGE patients

Patient	Diagnosis	Medication doses (mg) and frequency	Sex (F, M)	Age (yrs.) at seizure onset	Age at start of study	Habitual sleep time	Habitual wake time	Usual p.m. med time	Usual a.m. med time	Seizure types/description
1	Probable JME	VPA sprinkles 750 pm, 625 am	M	8	22	2 AM	10 AM	10 PM	10 AM	Possible myoclonus early in course; later absence and GTCS, but none for years prior to the study
2	IGE unspecified	LTG 300 bid TPM 25 bid	M	8	23	1 AM	10 AM	10 PM	10 AM	GTCS on awakening, some possibly preceded by irregular jerking
3	Probable JME	LTG 100 qpm	F	16	22	1 AM	9 AM	9 PM	none	"aura"—anxiety, myoclonic jerks, GTCS, photosensitivity
4	JME	LTG 250 mg qam, 200 mg qpm]	F	22	28	1 AM	9 AM	7 PM	7 AM	rare GTCS, myoclonus on CBZ only, full control on LTG
5	JME	VPA 250 bid	F	17	18	1 AM	10 AM	10 PM	10 AM	Frequent myoclonic jerks and GTCS while on CBZ or OXC, seizure free on VPA

JME—juvenile myoclonic epilepsy; LTG—lamotrigine, TPM—topiramate, VPA—valproic acid/divalproex; GTCS—generalized tonic-clonic seizures; CBZ—carbamazepine; OXC—oxcarbazepine