Laterality and location influence catamenial seizure expression in women with partial epilepsy

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ABSTRACT

Objective: The temporal distribution of seizures in women with localization-related epilepsy occurs periodically according to a model “clock” with the peak phase of occurrence corresponding to menstrual onset. The location and laterality of the epileptic lesion as well as patient age may affect periodicity.

Methods: Baseline data from seizure and menstrual diaries of ~3 months duration were obtained from 100 women enrolled in a trial of hormonal therapy for localization-related epilepsy. Durations of individual cycles were normalized to a common menstrual phase and period. Normalized data were then combined to create distributions evaluated by localization (lobar: temporal [TL], extratemporal [XL], multifocal [MF], unknown), lateralization (left, right, bilateral, unknown), and age. Distributions were evaluated with analysis of variance (ANOVA) and curve-fitted by nonlinear least squares cosinor analysis.

Results: A total of 71 patients had TL (left = 25, right = 29, bilateral = 17), 10 XL, 14 MF, and 5 unknown seizure foci. XL and MF seizures occurred randomly across the 28-day cycle. TL seizures (left = 875, right = 706) occurred nonrandomly (ANOVA $p = 0.0003$) and cyclically with peak occurrence near onset of menses ([value $\pm$ SD] peak = 1.6 ± 2.3 days, period = 27.0 days). Left-side TL seizures peaked cyclically at onset of menses (ANOVA $p = 0.04$, peak = 0.0 ± 3.0 days, period = 30 days); right-side TL seizures occurred randomly. Age did not have a cyclical effect. Women below the median age had a significantly higher seizure rate than those above the median age.

Conclusion: Circalunar rhythms of seizures in women, and therefore, possibly strategies of hormonal treatments of catamenial epilepsy, vary with the neuroanatomic substrate of the seizure focus. *Neurology*® 2009;73:223-227

GLOSSARY

ANOVA = analysis of variance; **HPG** = hypothalamo-pituitary-gonadal; **LH** = luteinizing hormone; **MF** = multifocal; **TL** = temporal; **XL** = extratemporal.

Past investigations on catamenial epilepsy have focused on establishing the existence and methodology of describing a relationship between seizure occurrence and the menstrual cycle.¹⁻⁵ In previous work, we established that seizures occur in significant circalunar rhythms linked to the menstrual cycle “clock.”⁶ We now focus on determining whether seizure periodicities are influenced by the laterality and focality of epilepsy.

The laterality and focality of epilepsy may influence reproductive endocrine function.⁷ Specifically, there is evidence to suggest that left-sided temporolimbic, but not nontemporal, epilepsy is associated with polycystic ovarian syndrome; right-sided temporolimbic epilepsy is associated with hypothalamic amenorrhea.⁷ This may relate to a lateralized asymmetry in reproductive endocrine regulation by the hypothalamo-pituitary-gonadal (HPG) axis⁸ and to a preferential ipsilateral activation of hypothalamic nuclei by unilateral amygdaloid seizures.^{7,9} There is also evidence that hormonal influences on seizure occurrence may show a lateralized

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Table 1 Patients (seizures) by lobar location and side					
Location	Left	Right	Bilateral	Unknown	Total
TLE	25 (875)	29 (730)	17 (469)	0	71 (2,074)
XTLE	5 (135)	1 (49)	4 (36)	0	10 (220)
Multifocal	4 (282)	6 (465)	4 (360)	0	14 (1,107)
Unknown	0	0	0	5 (95)	5 (95)
Total	34 (1,292)	36 (1,244)	25 (865)	5 (95)	100 (3,498)

TLE = temporal lobe epilepsy; XTLE = nontemporal lobe epilepsy; multifocal = both temporal and nontemporal foci.

asymmetry. Specifically, a previous study determined that left-sided temporal lobe epilepsy was more likely to occur in a catamenial pattern in women of childbearing age than right-sided temporal lobe epilepsy.⁹

In the present study, we determined pretreatment seizure periodicity as determined by the menstrual clock, provided by a common phase marker of the onset of menstrual bleeding, in a sample of women participating in a prospective, multicenter trial of progesterone treatment for partial epilepsy. We compare the resulting temporal patterns of seizure expression in association with the lobar location and side of the epileptic focus. Since aging¹⁰ may also have interactions with the regulation of the HPG axis, effects on seizure rhythms were evaluated by comparing seizure distributions from groups above and below the median age.

METHODS Subjects. Human investigation committees at the study sites approved the treatment protocol, and patients participated only after informed consent. These data were collected from the first 100 consecutive women with localization-related epilepsy who participated in the baseline phase of an ongoing multicenter, prospective, double-blind investigation of the use of hormonal treatment for medically intractable seizures.¹ Ages ranged from 13 to 45 years (mean $\pm$ SD: 33.1 $\pm$ 6.9). The women had intractable seizures despite trials of at least 2 antiepileptic drugs. Antiepileptic drug use was as follows: monotherapy 37 (carbamazepine 9, phenytoin 8, lamotrigine 7, topiramate 2, oxcarbazepine 2, single cases on other monotherapies 9) and combination therapy with 2 antiepileptic drugs 50 (polytherapy 10, no therapy 3). Subjects had at least 2 seizures each month. Catamenial epilepsy was not a selection criterion, although 35% of women were designated as having a catamenial pattern of seizure exacerbation as calculated by established criteria (42.8% menstrual pattern/C1, 22.9% ovulatory/C2, 34.2% luteal/C3).³ None of the subjects took any form of hormonal supplement or was on a hormonal form of contraceptive.⁶ Data evaluated in the current study focus specifically on the de-identified pretreatment seizure and menstrual cycle diaries provided by each patient.

Patients were classified by the lobar location (temporal, extratemporal, multifocal, and unknown) and side (left, right, bilateral, unknown) of epileptic foci by standard clinical criteria.

Localization was determined by site investigators independently from seizure pattern analysis. The laterality and focality of a seizure focus was determined by interictal EEG and collaborated by ictal EEG, MR anatomic imaging, interictal or ictal SPECT, or PET scan findings. Focality was listed as unknown where there was discordance among interictal EEG and other modalities.

Data analysis. To overcome the obstacles in pattern analysis caused by the variability in the duration of menstrual cycles, we normalized seizure diary data in reference to a common menstrual phase and period, a menstrual clock with a phase marker of the first day of menstrual bleeding.⁶ This method not only allowed combining data with the use of a common menstrual phase marker and period, it also accurately accounted for multiple daily seizures in those patients who experienced catamenial seizure clustering.

The resulting temporal patterns were evaluated with analysis of variance (ANOVA) to determine randomness of distribution. Nonrandom distributions were evaluated with cosinor-nonlinear least squares analysis^{11,12} to determine periodicity of rhythms within serial data. The algorithm (Pulse, University of Virginia¹³) iteratively summarizes time series data to a series of cosine functions described by period, amplitude, phase, and mean within specified confidence limits. Rhythms were designated significant when amplitude exceeded its lower confidence limit by a single-tailed p value < 0.05 .

RESULTS Table 1 shows the distribution of patients and seizures by lobar location and side of epileptic foci. Five subjects with unknown localization were not evaluated further. The mean rate of seizures varied among temporal, extratemporal, and multifocal foci (ANOVA $p < 0.0001$) (figure, A). Seizures from multifocal (ANOVA $p = 0.92$) and extratemporal lobe ($p = 0.29$) foci were distributed randomly across the normalized 28-day cycle. Seizures from temporal lobe foci occurred in a monophasic, nonrandom distribution ($p = 0.0003$) with peak occurrence corresponding to the onset of the menstrual phase of the 28-day cycle (value $\pm$ SD, peak = 1.6 $\pm$ 2.3 days, period = 27.0 days).

We restricted the remainder of our analyses to unilateral temporal lobe foci (n patients [seizures] = 54 [1,605], table 2). Age was distributed evenly by the side of seizure focus. The distribution of seizures across the 28-day cycle differed by the side of the temporal seizure focus (figure, B). Whereas seizures from patients with left-sided foci occurred cyclically and maximally at onset of menses (ANOVA $p = 0.04$, peak = 0.0 $\pm$ 3.0 days, period = 30.0 days), seizures from patients with right-sided foci occurred randomly with respect to the 28-day cycle (ANOVA $p = 0.90$).

The median age of patients with unilateral temporal foci was 40 years (table 2). Among patients with unilateral temporal foci, seizures occurred at a significantly higher daily rate in patients with age below the median in a phase independent fashion (ANOVA $p < 0.0001$) (figure, C).

Figure Distribution of mean seizures/menstrual cycle day $\pm$ SD by (A) lobar localization: Patients with seizure foci of the temporal lobe (tle), extratemporal foci (xtle), or multifocal localization (mfe); (B) patients with temporal lobe foci of the left or right sides; and (C) patients with temporal lobe foci divided into 2 groups above and below the median age

Day 0 corresponds to onset of menstrual bleeding.

DISCUSSION This study determined that the circalunar rhythms of seizures in women vary with the neuroanatomic substrate of the seizure focus. Temporal lobe seizures, especially left-sided foci, are more susceptible to circalunar rhythmic occurrence than those arising from extratemporal or multifocal foci. These findings supplement our early report of this same

Table 2 Characteristics of the temporal lobe foci subgroup by side of epileptic focus and by median age group

Category	Left	Right
No. patients (seizures)	25 (875)	29 (730)
Age, y		
Mean (SD)	37.9 (6.2)	38.8 (7.0)
Median	39	41
p Value	0.66	
Category (median age = 40 y)	<40	$\geq$ 40
No. patients (seizures)	25 (963)	29 (717)
Age, mean (SD)	32.8 (5.1)	43.2 (2.9)

patient sample which described predominant circalunar rhythms of seizure occurrence in women with partial epilepsy.⁶ Our findings agree with earlier reports that catamenial epilepsy is substantially and statistically significantly more common among women with left temporal foci than among those with right temporal foci.⁹ We also find that age affects overall seizure rate in this sample; youth facilitates seizure occurrence across the 28-day cycle. Because this factor is phase-independent, we conclude that the modulatory effect of age may arise from factors outside the cyclic effects of the HPG axis.

Because the techniques presented here rely on relatively short durations of group data to calculate circalunar seizure patterns, group measures of rhythmicity do not address adequately the important question of which individual patient can be considered to have catamenial epilepsy. Nevertheless, it can calculate the degree to which a population expresses seizures rhythmically, and thus compare patterns of seizure expression among groups. Although the progesterone treatment protocol upon which the current study is based did not use catamenial seizures as an inclusion criteria, we acknowledge that recruitment could favor women with catamenial epilepsy. Regardless of this possible bias, just over one-third of this sample had catamenial seizures according to previously published criteria in which cycle-associated seizures occur in $\sim$ 2:1 ratio above baseline.³ The prominent peak of group seizure occurrence at the onset of menses (C1) is probably due to the greater proportion of women in the sample with a menstrual-onset pattern of seizure expression in the catamenial group.

The underpinnings of lateralization of catamenial seizure expression are not known, but we hypothesize that the functional activity of the HPG axis mirrors side-to-side differences in activities of upstream afferents. In this model, normal HPG function is the inte-

grated contribution of left and right hypothalami. Differential activation, whether of physiologic or pathologic origin, may have different consequences. From animal models of limbic seizures, we know that unilateral seizures triggered by amygdalar stimulation asymmetrically affect hypothalamic regions involved in gonadotropin secretion; seizures preferentially activate ipsilateral rather than contralateral hypothalamic nuclei.⁷ Differential activation of hypothalamic nuclei, in turn, can have hormonal consequences. Accordingly, the side of the epileptic lesion influences the patterning of reproductive hormone secretion in humans. In men with temporal lobe epilepsy, the ultradian pulsatile secretion of luteinizing hormone (LH) occurs at a higher rate in association with right temporal foci compared to left.^{14,15} Certain reproductive diseases distribute differently in women with partial epilepsy; left-sided spikes or seizure foci are more predominant among those with polycystic ovary disease, and right-sided spikes or foci more with hypogonadotropic hypogonadism.^{8,9} A previous study determined that left-sided temporal lobe epilepsy was more likely to occur in a catamenial pattern in women of childbearing age than right-sided temporal lobe epilepsy.⁹

Interactions with regulatory systems outside the HPG axis may also demonstrate lateralization of function. In hamsters, activation of LH-containing neurons occurs much more strongly with activation of the ipsilateral rather than the contralateral supra-chiasmatic nucleus,¹⁶ which in turn affects circadian locomotor activities. In men with temporal lobe epilepsy, right temporal seizures were associated with phase delays and left temporal seizures with phase advances in the daily time of peak concentration of serum LH.¹⁷

The finding that the influence of reproductive hormones on seizure occurrence relates to the laterality and focality of the epilepsy may be particularly important if this relationship pertains not only to our understanding of pathophysiology but also to the design of hormonal treatment trials for women with epilepsy. The ongoing NIH-sponsored trial of progesterone therapy for women with partial epilepsy may demonstrate different responses to treatment depending on the location and side of the epileptic lesion.

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DISCLOSURE

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APPENDIX

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