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Variation of Seizure Frequency with Ovulatory Status of Menstrual Cycles

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Abstract

Purpose—To determine if seizure frequency differs between anovulatory and ovulatory cycles.

Methods—The data came from the 3-month baseline phase of an investigation of progesterone therapy for intractable focal onset seizures. Of 462 women who enrolled, 281 completed the three-month baseline phase and 92 had both anovulatory and ovulatory cycles during the baseline phase. Mid luteal progesterone levels ≥ 5 ng/ml were used to designate cycles as ovulatory. Among the 92 women, average daily seizure frequency (ADSF) for all seizures combined and each type of seizure considered separately (generalized tonic clonic seizures – 2°GTCS, complex partial seizures – CPS, simple partial seizures – SPS) were compared between anovulatory and ovulatory cycles using paired t-tests. A relationship between the proportional differences in ADSF and estradiol/progesterone (EP) serum level ratios between anovulatory and ovulatory cycles was determined using bivariate correlational analysis.

Key Findings—ADSF was 29.5% greater for 2°GTCS during anovulatory than during ovulatory cycles. ADSF did not differ significantly for CPS or SPS or for all seizures combined. Proportional differences in anovulatory/ovulatory 2°GTCS ADSF ratios correlated significantly with differences in anovulatory/ovulatory EP ratios. Among the 281 women, the three seizure types did not differ in ovulatory rates but EP ratios were greater for cycles with 2°GTCS than partial seizures only.

Significance—Seizure frequency is significantly greater for 2°GTCS, but not CPS or SPS, during anovulatory cycles than ovulatory cycles. Since the proportional increases in 2°GTCS

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The remaining authors have nothing to disclose.

frequency during anovulatory cycles correlate with the proportional increases in EP level ratios, these findings support a possible role for reproductive steroids in 2°GTCS occurrence.

Keywords

Epilepsy; reproductive; hormones; anovulation; menstrual cycle

Introduction

Reproductive steroids have neuroactive properties that can affect neuronal excitability and seizures (Herzog 2008a). Although these effects are complex, basic science and experimental animal models have identified a number of possible mechanisms. Estradiol may promote seizures by increasing the number of excitatory synapses on hippocampal dendritic spines as well as the number of these spines and by potentiating NMDA mediated neurotransmission (Woolley et al. 1997). Estradiol may also increase hippocampal excitability by the induction of brain derived neurotrophic factors (Scharfman et al. 2003). In contrast, progesterone may inhibit seizures via reduced metabolites such as tetrahydroprogesterone (allopregnanolone) that act as potent positive allosteric modulators at the GABA_A receptor (Reddy et al. 2001; Frye et al. 2002). The neurosteroid sensitivity of GABA_A receptors on dentate granule cells, however, may be diminished in animal models of temporal lobe epilepsy (Sun et al. 2007). Further, progesterone can regulate the subtype composition of the GABA_A receptor to modulate its sensitivity to synaptic GABA and pharmacologic input (Hsu & Smith 2003; Smith et al. 1998; Maguire et al. 2005). Therefore, the neuroactive properties of reproductive steroids and the variation of the serum levels and ratios of these steroids across the menstrual cycle may contribute to variations in seizure frequency in relation to the phases of the menstrual cycle (Herzog 2008a; Herzog et al. 1997; Herzog et al. 2004). This occurrence is commonly known as catamenial seizure exacerbation or catamenial epilepsy (Herzog 2008a; Herzog et al. 1997; Herzog et al. 2004).

Hormonal serum level ratios differ in relation to the ovulatory status of menstrual cycles (Herzog 2008a). Anovulatory cycles have higher EP ratios during the luteal phase than do ovulatory cycles (Herzog 2008a). Anovulatory cycles may also show a different pattern of catamenial seizure exacerbation than ovulatory cycles (Herzog 2008a; Quigg et al. 2008). Anovulatory cycles are more common among women with epilepsy than in the general population (Herzog 2008b; Cummings et al. 1995; Backstrom 1976). It has been suggested in some studies that anovulatory cycles may be associated with more seizures than ovulatory cycles (Herzog et al. 1997; Backstrom 1976; Mattson et al. 1981). Two of these studies were very small (Backstrom 1976; Mattson et al. 1981) and one compared seizure frequencies in two separate groups of women (Herzog et al. 1997). The purpose of this investigation was to determine if women who have both anovulatory and ovulatory cycles experience more seizures during their anovulatory cycles and, if so, whether differences in seizure frequency might be related to differences in estradiol/progesterone ratios.

Methods

Study Design

This was a multicenter, prospective, observational investigation.

Standard protocol approvals, registrations, and patient consents

This study was approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center and by the IRBs of all participating sites. Written informed consent was obtained from all patients or parents/guardians in the case of minors.

Subjects

The data came from the 3-month baseline phase of a double-blind, placebo controlled randomized investigation of adjunctive cyclic progesterone versus placebo therapy for intractable focal-onset seizures. Of 462 women who enrolled, 281 completed the three-month baseline phase. Of these, 92 who had both anovulatory and ovulatory cycles were utilized for the analysis to compare seizure frequency between anovulatory and ovulatory cycles. All of the enrolled women had clinical and EEG documented intractable focal onset seizures (>2/month). Epilepsy laterality (left, right, bilateral independent, unknown) and focality (temporal, non-temporal, both, unknown) were established as far as possible from available EEG and imaging (interictal/ictal SPECT, PET, MR) reports and were listed as unknown in case of discordance. Inclusionary criteria required that they be established on a stable antiepileptic drug regimen for at least one month and have at least one drug on that regimen documented to be in therapeutic range at the time of entry into the study. The women were required to have menstrual cycle intervals of 23–35 days. Inappropriate cycle intervals were the reason for dropout of 45 women during the baseline phase. This constituted 29.61% of baseline phase dropouts. Exclusionary criteria also included the use of prescribed or OTC reproductive hormones.

Procedures

The women received standardized instructions for charting seizure occurrence, type of seizure and date of onset of menstrual flow on printed calendars for three consecutive menstrual cycles. During the mid luteal phase of each cycle, 4–10 days before menstrual onset, a blood sample was drawn for batched measurement of serum estradiol and progesterone levels in order to determine the ovulatory status of cycles. Estradiol was measured by immunoassay. Progesterone was measured by liquid chromatography tandem mass spectrometry.

The data comparing seizure frequencies between anovulatory and ovulatory cycles came from the seizure-menses charts of the 92 women who were determined to have both anovulatory and ovulatory cycles during the three-month baseline phase. Mid luteal progesterone levels ≥ 5 ng/ml were used to designate cycles as ovulatory. Where two of the three cycles were anovulatory or ovulatory, average daily seizure frequency (ADSF) was calculated from combined cycle data. ADSF was compared for the 92 women between the days of anovulatory and ovulatory cycles for all seizures combined as well as for each seizure type (secondary generalized tonic clonic seizures – 2°GTCS, complex partial

seizures – CPS, simple partial seizures – SPS). Changes in ADSF between anovulatory and ovulatory cycles were related to changes in E/P ratios for each seizure type

To put the results of the comparisons carried out for the group of 92 women into the context of the entire group of 281 women who completed the baseline phase, rates of each seizure type and of anovulatory cycles, as well as EP ratios were compared for the three seizure types between the two groups of women. Seizure type designation was based on the most severe seizure type during any single cycle (2°GTCS > CPS > SPS).

Statistical Analysis

Demographic and epilepsy characteristics that were continuous variables were compared for the three seizure types in the 92 subjects who had both anovulatory and ovulatory cycles using ANOVA and Bonferroni post hoc tests. Epilepsy and AED characteristics that were reported as proportions were compared using chi square analysis. ADSFs for all seizures combined and each type of seizure considered separately (2°GTCS, CPS, SPS) were determined for anovulatory and ovulatory cycle days for each woman and comparisons between anovulatory and ovulatory cycles for all of the seizure types were performed using paired t-tests. A relationship between the proportional differences in ADSF, i.e. anovulatory/ovulatory ADSF ratios, and the midluteal EP levels, i.e. anovulatory/ovulatory EP ratios, was determined using bivariate correlational analysis.

Data from the 281 subjects who completed the baseline phase were used to 1) compare ADSF between anovulatory and ovulatory cycles for each seizure type using appropriate parametric or nonparametric tests for independent samples, 2) compare proportions of anovulatory cycles among the seizure types using chi square analysis, and 3) determine correlations for proportional changes in ADSF and E/P ratios between anovulatory and ovulatory cycles for each seizure type using bivariate correlational analysis.

Results

The demographic, epilepsy and antiepileptic drug characteristics are presented for the 92 women who had both anovulatory and ovulatory cycles in Table 1. Separate data are not presented for anovulatory and ovulatory cycles since each woman served as her own control. The demographic, epilepsy and AED characteristics did not differ significantly among 2°GTCS, CPS and SPS. A nonparametric sign test did not show any significant directional change in AED levels overall between anovulatory and ovulatory cycles. 2°GTCS occurred in 29.3%, i.e. 27 of the 92, women. CPS occurred in 67 (72.8%) and SPS in 31 (33.7%). The Levene test was consistent with homogeneity of variances between groups of anovulatory and ovulatory data. ADSF was 29.5% greater for 2°GTCS during anovulatory than during ovulatory cycles (anovulatory: $.237 \pm .488$ v ovulatory: $.183 \pm .440$; $t = 2.324$, $p = .028$) (Table 2). ADSF did not differ significantly for CPS or SPS or for all seizures combined. The likelihood of finding a significant difference, i.e. power of the comparison, was .1068 for CPS and .0506 for SPS. There was a significant correlation between the proportional changes in ADSF between anovulatory and ovulatory cycles and the severity of seizure type using the sequence 2°GTCS (average proportional change: 29.51%) > CPS (7.23%) > SPS (1.60%) (Spearman's $\rho = 0.194$, $p = .032$). Anovulatory/ovulatory 2°GTCS ADSF ratios

correlated significantly with anovulatory/ovulatory EP serum level ratios (Spearman $\rho = .577$, $p = .002$) (Figure 1). No significant correlation was demonstrated for CPS and SPS considered separately although there was a trend (Spearman $\rho = .349$; $p = .095$) for partial seizures considered combined.

Among the 281 women with epilepsy, 2°GTCS occurred in 37.4%, CPS in 81.1% and SPS in 38.4%. These percentages were a little greater than but not significantly different from the distribution among the 92 women. The percent of anovulatory cycles that had 2°GTCS did not differ significantly between the 281 women who completed the baseline phase and the 92 women who were the focus of this analysis ($142/412 = 34.5\%$ v $50/157 = 31.8\%$; $\chi^2 p = \text{N.S.}$). Among the 281 women, the ADSF for 2°GTCS was three times greater for anovulatory than ovulatory cycles ($.467 \pm .747$ v $.155 \pm .268$) but the Levene test for homogeneity of variances was significant at $p < .001$, prompting nonparametric analysis. By non-parametric Wilcoxon rank-sum test, ADSF for 2°GTCS showed a trend to be greater for anovulatory than for ovulatory cycles (median [1st quartile, 3rd quartile], anovulatory: .115 [.036, 0.365] v ovulatory: .070 [.037, 0.149]; $z = 1.856$, $p = .063$). There was no significant difference for CPS or SPS. Rates for anovulatory cycles were similar ($\chi^2 p = \text{N.S.}$) for cycles having 2°GTCS (26.0%), CPS (28.8%) and SPS (26.3%) as the most severe seizure type. EP serum level ratios, however, were significantly greater for cycles with 2°GTCS than for those with partial (CPS and SPS) seizures only (Wilcoxon rank-sum test: 3.450 [1.920, 6.987] v 2.087 [1.462, 3.615]; $z = 2.136$, $p = .033$).

Discussion

The critical questions that need to be addressed concerning the importance of hormones in epilepsy are whether hormones play a substantive role in seizure occurrence and whether hormones have a substantive role in treatment. Investigations into the chronobiologic aspects of seizure occurrence suggest that seizures do not occur randomly in the majority of individuals with epilepsy (Herzog 2008a). They tend to cluster (Herzog 2008a; Fowler et al. 2006). Clusters may occur with temporal rhythmicity in a significant proportion of men (Almqvist 1955) and women with epilepsy (Almqvist 1955; Quigg et al. 2008). In some women, perhaps one-third, the periodicity may conform to that of the menstrual cycle, in which case it is called catamenial epilepsy (Herzog 2008a; Herzog et al. 1997; Herzog et al. 2004). Seizures may show exacerbation during various phases of the menstrual cycle (Herzog 2008a; Herzog et al. 1997; Herzog et al. 2004). Seizures tend to increase perimenstrually, possibly related to the rapid premenstrual withdrawal of progesterone, and mid cycle, perhaps in relation to the pre-ovulatory estrogen surge, during ovulatory cycles (Herzog 2008a; Herzog et al. 1997; Herzog et al. 2004). Seizures may increase also during the entire second half or luteal phase, during anovulatory cycles, perhaps in relation to low progesterone levels relative to estrogen, or during some ovulatory cycles that have high EP ratios (Herzog 2008a; Herzog et al. 2008). Seizure frequency may be greater during anovulatory cycles (Backstrom 1976; Mattson 1981; Herzog et al. 1997) but large controlled prospective studies have been lacking.

This investigation identified 92 women with intractable focal-onset seizures who were on stable antiepileptic drug regimens and had both anovulatory as well as ovulatory cycles over

a span of three baseline phase cycles prior to randomization for a placebo controlled hormonal treatment trial. The selection of this group of women permitted each woman to act as her own control with regard to age, seizure types, duration of epilepsy and antiepileptic drug regimen. Moreover, a nonparametric sign test did not show any significant directional change in AED levels overall between anovulatory and ovulatory cycles. In these 92 women, seizure frequency was substantially (29.5%) and significantly greater for 2°GTCS, but not CPS or SPS, during anovulatory cycles than during ovulatory cycles. Since the proportional increases in anovulatory versus ovulatory 2°GTCS frequencies correlated with the proportional increases in mid luteal EP serum level ratios, these findings support a possible role for reproductive steroids in 2°GTCS occurrence.

The findings are consistent with previous studies that have suggested a greater seizure frequency with anovulatory cycles and high EP ratios (Backstrom 1976, Mattson et al. 1981 and Herzog et al 1997). Backstrom (1976) studied in great detail 9 cycles, 6 ovulatory and 3 anovulatory, in 7 women and found a positive correlation between seizure frequencies and serum EP ratios during ovulatory cycles and between seizure frequencies and serum estradiol levels during anovulatory cycles. He demonstrated lower seizure frequencies during phases of high progesterone in ovulatory cycles and higher seizure frequencies during phases of high estradiol during anovulatory cycles. He found that these relationships were statistically more significant for 2°GTCS than partial seizures. He could not relate changes in seizure frequency to changes in antiepileptic drug levels (Backstrom et al 1979). Mattson (1981), in a study of 14 women with epilepsy over 3–6 consecutive cycles, reported that “seizure frequency was much greater for anovulatory cycles than ovulatory cycles ($p < 0.05$).” Herzog et al. (1997) compared a group of 86 women with intractable seizures who had anovulatory cycles with a group of 98 who had ovulatory cycles during a single prospectively recorded menstrual cycle (Herzog et al. 1997). Anovulatory cycles in that investigation were associated with 47.3% greater seizure frequency overall and a 290% higher level for 2°GTCS. The comparison of independent samples for 281 women in this investigation shows a similar 301.2% greater ADSF for 2°GTCS with anovulatory cycles. In the paired comparison for the group of 92 women in the present investigation, the difference in ADSF for 2°GTCS between anovulatory and ovulatory cycles is much more conservative but significant at 29.5%. The reason for the difference in the level of findings is not certain but could relate to the greater level of control provided by paired comparisons as opposed to independent comparisons. This possibility is supported by the lack of homogeneity in ADSF distributions found between anovulatory and ovulatory cycles in the 281 women that required nonparametric analysis.

The difference in ADSF findings between cycles with 2°GTCS versus partial seizures only is not known. This distinction between 2°GTCS versus partial seizures is consistent with Backstrom’s findings (1976). Differences could not be related significantly to epilepsy characteristics (laterality, focality, age of onset or duration) or antiepileptic drug type and mid-luteal level. The effect may relate to the level of seizure propagation as suggested by the apparent correlation between the proportional changes in anovulatory/ovulatory cycle ADSF and the presumed extent of propagation as suggested by the sequence of 2°GTCS>CPS>SPS (Table 2). The difference may also relate to the significantly greater EP ratios associated with 2°GTCS cycles.

Although seizure frequency showed a relationship to ovulatory status for 2°GTCS, ovulatory status did not differ in frequency between cycles with 2°GTCS versus partial seizures only. The rates of anovulation among the women with epilepsy in this study (26.0–28.8%), regardless of seizure type, are somewhat less than the rates reported in some other studies. Bauer et al. (1998) found a rate of 31.8% (42 of 132 cycles) in women with focal onset seizures. Cummings et al. (1995) found 35% as compared to 8% in controls. In our own previous study, we found 39% (39 of 100 cycles) (Herzog and Friedman 2002). Our present finding is likely to be an underestimate of the rate in the community because women with cycle intervals of <23 or >35 days were excluded from the investigation and, based on our earlier findings (Herzog and Friedman 2002), this would add another 10%. All of these epilepsy estimates surpass the expected rate of anovulation of about 9% (20 of 221 cycles) in the general population (Haiman et al. 2002). Therefore, the finding of an association between increased 2°GTCS frequency and anovulatory cycles and the existence of a greater frequency of anovulatory cycles among women with epilepsy suggest that greater attention be devoted to the ovulatory status of women with epilepsy, not only with regard to general reproductive health and fertility but also for comprehensive seizure management.

If hormones play a role in seizure occurrence, there may also be a role for hormones in seizure therapy. To date, two small open label trials of adjunctive natural progesterone supplement have suggested some possible efficacy (Herzog 1986; Herzog 1995; Herzog 1999) as has a prospective phase 2b multi-center, double blind placebo controlled trial of the synthetic allopregnanolone analogue ganaxolone that showed a significantly greater reduction in seizure frequency in the treatment arm than in the placebo group and a greater proportion of 50% responders (Marinus Pharmaceuticals, Inc. 2009). The phase 3 multicenter, randomized, placebo-controlled, clinical trial of progesterone supplement that generated the data for this report has been completed and efficacy results are pending.

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Appendix

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Figure 1.

In a comparison of anovulatory to ovulatory cycles, there is a significant correlation between the proportional increase in average daily seizure frequency for secondary generalized tonic-clonic seizures during anovulatory cycles (Anov/Ov ADSF ratio) and the proportional increase in serum estradiol to progesterone (Anov/Ov EP ratio) ratios (Spearman's rho = 0.577; $p = 0.002$).

Table 1

Demographic, Epilepsy and Antiepileptic Drug Characteristics Overall and by Seizure Type

	All Seizure Types (N = 92)	2°GTCS (N = 27)	CPS (N = 67)	SPS (N = 31)
Age (years)	31.79 ± 8.21	29.93 ± 8.74	32.44 ± 8.06	33.08 ± 7.57
BMI	26.17 ± 7.13	24.60 ± 7.62	26.50 ± 7.22	27.85 ± 5.59
Age of Epilepsy Onset (years)	12.49 ± 11.39	10.81 ± 13.21	13.45 ± 10.53	12.15 ± 11.16
Duration of Epilepsy (years)	17.81 ± 11.19	17.00 ± 13.04	18.37 ± 10.57	17.23 ± 10.18
Epilepsy Focality	T: 69.6% NT: 14.1% Both: 13.0% Unk: 3.3%	T: 59.3% NT: 22.2% Both: 14.8% Unk: 3.7%	T: 76.9% NT: 11.5% Both: 11.5% Unk: 0.0%	T: 61.5% NT: 9.7% Both: 15.4% Unk: 13.4%
Epilepsy Laterality	L: 37.0% R: 30.4% Bilat: 28.3% Unk: 4.3%	L: 29.6% R: 22.2% Bilat: 44.4% Unk: 3.7%	L: 38.5% R: 32.7% Bilat: 26.9% Unk: 1.9%	L: 46.2% R: 38.5% Bilat: 0.0% Unk: 15.3%
Antiepileptic Drugs	CBZ: 5; GBP: 1; LEV: 4; LTG: 7; No AED: 1; OXC: 2; PHT: 4; TPM: 4; VPA: 1; ZNS: 1 Poly: 62	CBZ: 2; GBP: 0; LEV: 1; LTG: 1; No AED: 0; OXC: 1; PHT: 2; TPM: 3; VPA: 0; ZNS: 1 Poly: 16	CBZ: 4; GBP: 1; LEV: 4; LTG: 7; No AED: 1; OXC: 2; PHT: 4; TPM: 2; VPA: 1; ZNS: 1 Poly: 40	CBZ: 3; GBP: 1; LEV: 3; LTG: 4; No AED: 1; OXC: 2; PHT: 2; TPM: 1; VPA: 1; ZNS: 1 Poly: 12

Column headings: 2°GTCS, CPS, SPS refer to most severe seizure type

Epilepsy focality and laterality legend: T = temporal; NT = non temporal; L = left ; R = right ; Bilat = bilateral independent; Unk = unknown

Antiepileptic drug legend: CBZ = carbamazepine; GBP = gabapentin; LEV = levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; PHT = phenytoin; TPM = topiramate; VPA = valproate; ZNS = zonisamide; Poly = polytherapy

Table 2

Comparison of Seizure Frequencies between Anovulatory and Ovulatory Cycles

Seizure Type	Anovulatory ADSF	Ovulatory ADSF	Change in ADSF (%)	Paired t-value	p-value
All	.432 ± .669	.421 ± .643	2.61	0.388	0.699
2°GTCS	.237 ± .488	.183 ± .440	29.51	2.324	0.028
CPS	.341 ± .621	.318 ± .556	7.23	0.703	0.485
SPS	.318 ± .464	.313 ± .453	1.60	0.123	0.903

This table compares average daily seizure frequencies between the days of anovulatory and ovulatory cycles for all seizures combined and for individual seizure types. ADSF was 29.5% greater for GTCS during anovulatory than during ovulatory cycles (paired t = 2.324, p = .028). ADSF did not differ significantly for CPS or SPS or for all seizures combined.