

Original Articles

Interictal EEG discharges, reproductive hormones, and menstrual disorders in epilepsy
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Abstract

We evaluated reproductive endocrine function in women with unilateral temporolimbic epilepsy and normal control subjects to assess the effects of epilepsy, epilepsy laterality, and antiepileptic drug use on the cerebral regulation of hormonal secretion. The findings indicate that reproductive endocrine function differs between women with epilepsy and normal control subjects. Significant differences exist at all levels of the reproductive neuroendocrine axis, that is, hypothalamus, pituitary, and peripheral gland. Differences show significant relationships to the epilepsy itself as well as to medication use. Reproductive neuroendocrine changes occur in a stochastic manner such that the laterality of unilateral temporolimbic discharges is associated with predictable directional changes in hormonal secretion at all levels of the reproductive neuroendocrine axis. These directional changes are consistent with the finding that different reproductive disorders may develop in relation to left- and right-sided temporolimbic epilepsy. Hormonal changes can show close temporal relationship to the occurrence of interictal epileptiform discharges and may vary in relation to the laterality of the discharges. Antiepileptic drugs differ in their effects on reproductive hormone levels. There are notable differences between enzyme-inducing and noninducing drugs. Menstrual disorders are more common among women with interictal discharges as well as women with abnormal hormonal findings. *Ann Neurol* 2003;54:625-637
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The brain controls reproductive function primarily through the hypothalamic regulation of pituitary secretion.[1] Regions of the hypothalamus that are involved in the regulation, production, and secretion of gonadotropin-releasing hormone (GnRH) receive extensive direct connections from the cerebral hemispheres, especially from temporolimbic structures and most notably the amygdala.[1] Cerebral influences on the reproductive functions of the hypothalamopituitary axis, however, have received little systematic clinical inquiry.

Localization-related epilepsy, the most prevalent form of epilepsy in adults, most commonly originates in or at least involves temporolimbic cerebral structures such as the hippocampus and amygdala and is often termed temporolimbic epilepsy, or TLE.[2][3] Temporal lobe seizures commonly produce transient hormonal changes.[4][5] The unusually frequent occurrence of reproductive endocrine disorders and reproductive dysfunction among women with TLE[6][7] raises the consideration that recurrent or persistent interictal epileptiform disruption of temporolimbic activity may lead to chronically altered hypothalamopituitary regulation of gonadal secretion and promote the development of reproductive endocrine disorders.[8][9] The observation in women that left-sided TLE (LTLE) may be associated with polycystic ovarian syndrome (PCOS) and right-sided TLE (RTLE) may be associated with hypothalamic amenorrhea (HA, hypogonadotropic hypogonadism), moreover, suggests a lateralized asymmetry in this possible effect.[10] TLE, therefore, may serve as a model to assess the role of temporolimbic structures in the cerebral modulation of hormonal secretion and reproductive

function, as well as the role that cerebral dysfunction may have in the pathophysiology of certain reproductive endocrine disorders such as PCOS and HA, which are overrepresented in TLE but have generally been assumed to be of primary hypothalamic origin[8][9] or secondary to antiepileptic drug effects.[11]

The purpose of this investigation was to determine if whether (1) reproductive endocrine function differs between women with TLE and normal controls subjects; (2) reproductive endocrine function in women with TLE varies in relation to epilepsy itself and, in particular, the laterality of paroxysmal temporolimbic epileptiform discharges; (3) reproductive endocrine function in women with TLE varies in relation to antiepileptic drug use; (4) epilepsy effects can be distinguished from antiepileptic drug effects; (5) menstrual and reproductive endocrine disorders are more common among women with TLE than among normal controls; (6) lateralized asymmetries in the reproductive neuroendocrine system are associated with different reproductive endocrine disorders in women with left and right TLE; (7) interictal paroxysmal electroencephalogram (EEG) discharges are temporally related to changes in gonadotropin secretion; and (8) there is a relationship among abnormal interictal paroxysmal EEG discharges, reproductive endocrine dysfunction, and menstrual disorders.

Subjects and Methods

Abstract Subjects and Methods Results Discussion References

Research Design

This investigation compared reproductive and reproductive endocrine function between women with unilateral TLE and normal control subjects. Epilepsy-related variables under consideration included (1) laterality of the epileptic focus and (2) antiepileptic drug use. Reproductive function variables included menstrual cycle characteristics and level of sexual interest and function. Reproductive endocrine measures were selected to reflect function at the three principal regulatory levels of reproductive function - hypothalamus, pituitary gland, and peripheral gland. Hypothalamic function measures included luteinizing (LH) hormone and prolactin (PRL) pulse frequency (PF) and amplitude (PA). Pituitary function was assessed by serum LH, follicle-stimulating hormone (FSH) and PRL levels, as well as serum LH/FSH ratio. Peripheral gland measures were serum testosterone (T), estradiol (E2), and dehydroepiandrosterone sulfate (DHEAS).

Subjects

The experimental group consisted of 36 women between the ages of 18 and 40 years who had at least monthly complex partial seizures and EEG documented unilateral left-sided (n = 20) or right-sided (n = 16) temporal lobe interictal epileptiform discharges. EEG documentation was obtained in the preceding 3 months in all cases. The majority (24 out of 36) of the subjects had additional supportive evidence for the proposed unilateral temporal lobe focus in the form of asymmetric temporal lobe findings on magnetic resonance imaging volumetry, magnetic resonance imaging blood flow (perfusion study), or ictal single photon emission computed tomography. The experimental subjects included 27 antiepileptic drug-treated (carbamazepine, n = 8; phenytoin, n = 8; valproate, n = 2; gabapentin, n = 2; polytherapy, n = 7) and 9 untreated women, 6 of whom had never been treated and 3 who had discontinued medication at least 3 months before testing because of medication intolerance or lack of efficacy. The six previously untreated women included three who had long-standing complex partial seizures who had never been diagnosed and three with recent onset seizures who refused antiepileptic drug treatment. Three of the previously treated and one of the previously untreated women had a remote history

of generalized convulsive seizures. All treated women had at least one current serum antiepileptic drug level in the therapeutic range at the time of investigation. No subject had a known clinical seizure during the 24 hours before testing or during the study.

The control group consisted of 12 similarly aged women who were recruited by advertising in the community. They had negative histories for neurological and reproductive disorders, normal neurological and gynecological examinations, and normal EEGs. Frequency comparisons of menstrual disorders and PCOS features in the community versus women with unilateral TLE were carried out using information from the medical records of 100 consecutive women between 18 and 40 years of age, drawn from the practices of a primary care physician and a gynecologist. No subject took hormones, major tranquilizers, or antidepressants during the 3 months prior before to participation.

Procedures

All women were tested during the early to mid-follicular phase (Day 3-7) of the menstrual cycle. Beginning at 8:00 AM, 5cc blood samples were drawn at 10-minute intervals for 8 hours by means of an intravenous catheter that was placed in an arm vein. Simultaneous concomitant surface and sphenoidal EEG recording was carried out during the entire 8-hour sampling period. The schedule and content of meals were standardized for all subjects.

Menstrual Function Evaluation

Reproductive function was considered abnormal if women had menstrual disorder, hirsutism, or galactorrhea. Menstrual disorder was defined as amenorrhea (no periods for 6 months), abnormally short or long menstrual cycle intervals (less than 26 or more than 32 days), greater than 4-days variability in cycle intervals, or menometrorrhagia (bleeding between periods or periods lasting longer than 1 week) during the preceding year.[7][12] Polycystic ovarian syndrome was defined as hyperandrogenemia and menstrual, ultrasound, or endocrine (less than 5ng/ml midluteal progesterone level) evidence of anovulation.[7][13-15] Hypothalamic amenorrhea was diagnosed by amenorrhea or oligomenorrhea associated with low gonadotropin level and low LH response to GnRH stimulation test.[7][16] Sexual function was considered to be abnormal if Arizona Sexual Experience Scale (ASEX) questionnaire scores fell more than two standard deviations outside of the established norm.[17] These results are presented elsewhere.[18]

Hormone Analysis

Blood samples were centrifuged, the serum separated, and the samples frozen at -20°C until hormone assays were performed. Commercially available kits were used to assay the hormones. FSH, LH, and PRL were measured by standardized fluoroimmunoassay. All standards, controls, and subject samples were assayed in duplicate with a coefficient of variation of <10% considered acceptable. Testosterone, DHEAS, estradiol, and progesterone were assayed by radioimmunoassay kits purchased from Diagnostic Products Corporation. Intra-assay and interassay variabilities were determined for all assays and limited to 5 and 10%, respectively.

Reproductive Endocrine Evaluation and Pulse Definitions

Hormonal measures included luteinizing hormone pulse frequency (LHPF) and amplitude (LHPA), prolactin pulse frequency (PRLPF) and amplitude (PRLPA), baseline serum levels of LH, FSH, PRL, LH/FSH ratio, T, DHEAS, E2, and thyroid function tests, including thyrotropin

stimulating hormone (TSH), thyroxine (T4), and free thyroxine (FT4). LH and PRL pulses were defined by peak values that were both 20% and three coefficients of variation higher than preceding nadirs.[19] Pulses were verified by the Cluster Analysis software program for pulse detection.[20] A 2~2 cluster configuration and a t statistic of 2 for the upstroke and downstroke were used to maintain false-positive and false-negative error rates below 10%. The difference between nadir and peak values represented pulse amplitude. The number of pulses during 8 hours of measurement was the pulse frequency. Mean baseline LH and PRL referred to the average pulse nadir values.

Electroencephalogram Evaluation

The EEG verified that temporal epileptiform discharges were unilateral in subjects with epilepsy and that control subjects had normal recordings. The EEG also identified the precise time and duration of paroxysmal activity to permit analysis of a potential temporal relationship between electrophysiological discharges and the levels and patterns of gonadotropin and prolactin secretion.

Data Analysis

The data were derived from the measurement of six hormones in 12 female control subjects and 36 women with epilepsy, 27 of whom were on antiepileptic drugs (treated), and 9 on no medications (untreated). In addition to the baseline levels of the six hormones, pulse frequency and amplitude were determined for LH and PRL and the baseline ratio LH/FSH was computed for all subjects. The resulting 55 distributions formed from the 11 hormone parameters stratified into five groups (control, LTLE, RTLE, treated, and untreated subjects) were tested for normality. Central measures (mean, standard deviation, variance, and 95% confidence intervals) were computed and tabulated for all distributions. Assessment of variance, as well as mean, was considered to be particularly important because there is considerable evidence that limbic structures involved in TLE such as the amygdala may play an important role in bidirectional modulation of hypothalamic and pituitary endocrine function[21] and that abnormal limbic function may be manifest sometimes as significantly greater variation rather than altered mean values.[22-24]

Comparisons between the respective groups for statistically significant differences were performed using the appropriate pairwise multiple sample comparison procedures: Newman-Keuls for parametric and Kruskal-Wallis for nonparametric distributions. Two-sample comparisons were performed using unpaired t test or the rank sum test for parametric or nonparametric distributions, respectively. The p values were evaluated for two-tail outcome with a cutoff of 0.05 for statistical significance. In comparisons involving small numbers of subjects and also small numbers of epileptiform discharge-related hormonal changes, trends showing p values < 0.10 are reported as well. Comparisons of variances between women with TLE and normal controls were carried out using the F test. Correlations among hormonal parameters were tested using Pearson correlation analysis or Spearman's rank correlation procedure when comparing variables with dichotomous or nonparametric distributions. Testing for normality was carried out using the Shapiro-Wilk test. Of the 11 hormonal distributions 7 met the test of normality (p = 0.05); 3 additional distributions had p values between 0.05 and 0.10. Only estradiol deviated substantially from a normal distribution. Determination of hormonal parameters that were affected significantly by epilepsy laterality was carried out by stepwise multiple regression and stepwise logistic regression analyses, as well as Spearman's rank correlation procedure. Comparisons of proportions of women with reproductive dysfunction among groups and comparisons of the proportions of women with reproductive dysfunction who

had interictal paroxysmal EEG discharges among groups were carried out using Chi-squared analysis.

The means of the respective hormones were grouped by regulatory region (hypothalamus, pituitary gland, and peripheral endocrine gland) and are presented in tables and plots to demonstrate the relationships between (1) control versus subjects with TLE, (2) control versus LTLE and RTLE subjects, (3) control versus treated and untreated subjects with TLE, and (4) control versus separately considered treated and untreated, left and right TLE subjects.

Results

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Demographic Data

The four groups of women with TLE and the control group did not show any significant differences in age, duration of epilepsy, monthly seizure frequency, proportion with secondary generalized seizures or marital rate (Table 1). Twenty-five percent (5/20) of the women with LTLE were untreated at the time of the investigation as were 25% (4/16) of the women with RTLE.

Table 1. Demographics of Control Subjects and Women with Epilepsy

	Ctrl	LTLE M	LTLE NM	RTLE M	RTLE NM		
N	12	15	5	12	4		
Age (yr)		29.6 \pm 6.1	30.9 \pm 5.8	28.8 \pm 7.5	32.9 \pm 5.4	29.8 \pm 7.2	
Duration of epilepsy (yr)			-	8.2 \pm 6.4	5.4 \pm 4.8	7.7 \pm 5.4	6.2 \pm 4.1
Seizure frequency/month			-	7.2 \pm 4.8	5.2 \pm 4.5	6.8 \pm 5.4	4.6 \pm 4.4
Number (%) with SGMS			-	8 (53%)	2 (40%)	7 (58%)	2 (50%)

Values are mean \pm standard deviation. TLE, temporolimbic epilepsy; L/R, left/right laterality; M/NM, on medication/no medication; SGMS, history of secondary generalized motor seizures; Ctrl, controls.

Reproductive Endocrine Data

HYPOTHALAMIC PARAMETERS.

LHPF was significantly more variable among women with TLE than among controls (5.8 \pm 1.7 vs 6.0 \pm 0.7; $p < 0.01$; Table 2). Women with LTLE had higher LHPF than women with RTLE (6.5 \pm 1.5 vs 4.9 \pm 1.7; $p < 0.01$) (Table 3), regardless of medication use (untreated, 7.2 \pm 1.6 vs treated 4.0 \pm 0.8; $p < 0.01$ Fig 1).

Table 2. Reproductive Endocrine Function in Women with TLE and Control Subjects

	Control	TLE	p (mean)	p (variance)
N	12	36	t test	F test
Age (yr)		29.6 \pm 6.1	31.9 \pm 6.2	N.S. N.S.
Hypothalamus				
LHPF	6.0 \pm 0.7	5.8 \pm 1.7	N.S.	0.006
LHPA	2.1 \pm 0.6	2.4 \pm 1.0	N.S.	N.S.
PRLPF	3.4 \pm 1.2	3.2 \pm 1.1	N.S.	N.S.
PRLPA	3.0 \pm 1.5	4.6 \pm 6.1	N.S.	0.0002

	LH/FSH	0.93 ~ 0.35	0.92 ~ 0.50	N.S.	N.S.
Pituitary			N.S.		
	LH	4.7 ~ 1.5	4.9 ~ 2.5	N.S.	0.05
	FSH	5.2 ~ 0.9	5.9 ~ 2.0	N.S.	0.01
	PRL	9.2 ~ 3.2	8.4 ~ 3.6	N.S.	N.S.
Peripheral gland					
	Testo	32 ~ 11	29 ~ 14	N.S.	N.S.
	DHEAS	189 ~ 51	110 ~ 72	0.001	N.S.
	E2	35 ~ 6	22 ~ 8	0.001	N.S.

LHPF, luteinizing hormone pulse frequency; LHPA, luteinizing hormone pulse amplitude; PRLPF, prolactin pulse frequency; PRLPA, prolactin pulse amplitude; LH, luteinizing hormone; FSH, follicle stimulating hormone; PRL, prolactin; Testo, testosterone; DHEAS, dehydroepiandrosterone sulfate; E2, estradiol; TLE, temporolimbic epilepsy; N.S. not significant.

Table 3. Reproductive Endocrine Function in Women with Left and Right TLE and Control Subjects

	Ctrl	LTLE	RTLE		
N	12	20	16		
Age (yr)		29.6 ~ 6.1	30.4 ~ 6.0	31.5 ~ 6.2	
Hypothalamus					
	LHPF	6.0 ~ 0.7	6.5 ~ 1.5#	4.9 ~ 1.5#	
	LHPA	2.1 ~ 0.6	2.3 ~ 1.0	2.6 ~ 0.9	
	PRLPF	3.4 ~ 1.2	3.2 ~ 1.1	3.2 ~ 1.1	
	PRLPA	3.0 ~ 1.5	3.0 ~ 1.8	6.7 ~ 8.6	
	LH/FSH	0.93 ~ 0.35	1.1 ~ 0.5#	0.65 ~ 0.35#	
Pituitary					
	LH	4.7 ~ 1.5	5.6 ~ 2.6	4.1 ~ 2.3	
	FSH	5.2 ~ 0.9	5.3 ~ 1.8#	6.7 ~ 2.0#	
	PRL	9.2 ~ 3.2	8.1 ~ 3.4	8.8 ~ 3.8	
Peripheral gland					
	Testo	32 ~ 11	35 ~ 16##	22 ~ 9*##	
	DHEAS	189 ~ 51		122 ~ 83**	103 ~ 58**
	E2	35 ~ 6	25 ~ 7***##	18 ~ 6***##	

L or RTLE vs Ctrl:

* p 0.05

** p 0.01.

LTLE vs RTLE:

p 0.05

p 0.01.

For other abbreviations, see Table 2.

Figure 1. Reproductive endocrine function in women with epilepsy and controls. Hypothalamic parameters: LHPF was significantly more variable among women with TLE than among controls (6.0 ~ 0.7 vs 5.8 ~ 1.7; p < 0.01). Women with LTLE had higher LHPF than women with RTLE (6.5 ~ 1.5 vs 4.9 ~ 1.7, p < 0.01), regardless of medication use (untreated 7.2 ~ 1.6 vs 4.0 ~ 0.8, p < 0.01). LHPA was significantly higher among untreated women with TLE than among treated women (3.0 ~ 1.4 vs 2.3 ~ 0.7, p = 0.05) and controls (2.1 ~ 0.6, p < 0.05) without any significant laterality effect. PRLPF showed no significant findings in relation to epilepsy, epilepsy laterality, or medication use. PRLPA was significantly more variable among women with TLE than among controls (4.6 ~ 6.1 vs 3.0 ~ 1.5, p < 0.001). Variability was significantly greater among women with RTLE than among women with LTLE (6.7 ~ 8.6 vs 3.0

~ 1.8 , $p < 0.001$). PRLPA values were significantly greater for treated women with RTLE ($8.1 \sim 9.6$) than for untreated women with RTLE ($2.4 \sim 0.7$, $p < 0.05$), as well as women with LTLE (treated $2.9 \sim 1.7$, $p < 0.05$; untreated $3.5 \sim 2.3$, $p < 0.10$) and controls ($3.0 \sim 1.5$, $p < 0.05$). LH/FSH ratio was significantly greater for women with LTLE than for women with RTLE ($1.1 \sim 0.5$ vs $0.65 \sim 0.35$, $p < 0.01$), regardless of medication use (untreated $1.4 \sim 0.6$ vs $0.58 \sim 0.10$, $p < 0.01$). Pituitary parameters: LH was more variable among women with TLE than among controls ($4.9 \sim 2.5$ vs $4.7 \sim 1.5$, $p = 0.05$). The mean value was higher among untreated women with LTLE ($7.1 \sim 3.7$) than among treated women with LTLE ($5.0 \sim 1.9$; $p < 0.10$) and controls ($4.7 \sim 1.5$, $p < 0.10$), and more than twofold greater than the mean value for untreated women with RTLE ($3.1 \sim 0.9$, $p = \text{N.S.}$). FSH was more variable among women with TLE than among controls ($5.9 \sim 2.0$ vs $5.2 \sim 0.9$, $p = 0.01$). FSH was significantly higher for women with RTLE ($6.7 \sim 2.0$) than women with LTLE ($5.3 \sim 1.8$, $p < 0.05$). This lateralized difference among women with TLE was statistically significant only among treated women ($7.1 \sim 2.0$ vs $5.4 \sim 2.0$, $p < 0.05$). PRL did not show any significant finding in relation to epilepsy, epilepsy laterality, or medication use. Peripheral gland parameters: Testosterone levels were significantly greater for LTLE than RTLE ($35 \sim 16$ vs $22 \sim 9$, $p < 0.01$) as they were for controls ($32 \sim 11$ vs $22 \sim 9$; $p < 0.01$). There was no significant finding in relation to medication use. Estradiol levels were significantly greater among control subjects than women with epilepsy ($35 \sim 6$ vs $22 \sim 8$, $p < 0.001$) regardless of medication use (untreated $25 \sim 7$, $p < 0.01$; treated $21 \sim 7$, $p < 0.01$). E2 levels were significantly greater for LTLE than RTLE ($25 \sim 7$ vs $18 \sim 6$, $p < 0.01$) and each was significantly less than controls ($35 \sim 6$, $p < 0.01$). Lower E2 values with medication use were attributable to the use of enzyme-inducing drugs (E2 for barbiturate, carbamazepine, phenytoin users vs controls = $14.5 \sim 4.5$ vs $35.4 \sim 6.2$, $p < 0.001$) as opposed to non-enzyme-inducing drugs (E2 for gabapentin, lamotrigine, valproate users vs controls = $28.3 \sim 9.4$ vs $35.4 \sim 6.2$, $p = \text{N.S.}$). Untreated women with TLE had substantially lower E2 levels ($24.9 \sim 7.6$) than control subjects ($35.4 \sim 6.2$), albeit without statistical significance ($p < 0.20$). DHEAS values were significantly greater for controls than for women with TLE ($189.2 \sim 51.1$ vs $110.4 \sim 72.7$, $p < 0.001$). DHEAS values were significantly greater for control subjects ($189.2 \sim 51.1$, $p < 0.01$) and untreated women with TLE ($160.1 \sim 65.3$, $p < 0.01$) than for treated women with TLE ($93.8 \sim 68.2$). Lower DHEAS values with medication use were attributable to the use of enzyme-inducing drugs (DHEAS for barbiturate, carbamazepine, phenytoin users vs controls: $49.2 \sim 37.2$ vs $189.2 \sim 51.1$, t test $p < 0.001$) as opposed to non-enzyme-inducing drugs (DHEAS for gabapentin, lamotrigine, valproate users = $108.5 \sim 50.7$ vs $189.2 \sim 51.1$; t test $p = \text{N.S.}$). Values for enzyme-inducing drug users were significantly lower than for non-enzyme-inducing drug users ($49.2 \sim 37.2$ vs $108.5 \sim 50.7$, $p < 0.001$). LH, luteinizing hormone; LHPF, LH pulse frequency; LHPA, LH pulse amplitude; TLE, temporolimbic epilepsy; LTLE, left-sided TLE; RTLE, right-sided TLE; PRL, prolactin; PRLPF, PRL pulse frequency; PRLPA, PRL pulse amplitude; FSH, follicle-stimulating hormone; Testo, testosterone; DHEAS, dehydroepiandrosterone sulfate; E2, estradiol; CTRL, control.

[Normal View 36K | Magnified View 89K]

LHPA was significantly higher among untreated women with TLE than among treated women ($3.0 \sim 1.4$ vs $2.3 \sim 0.7$; $p = 0.05$) and controls ($2.1 \sim 0.6$; $p < 0.05$ Table 4) without any significant laterality effect. PRLPF showed no significant findings in relation to epilepsy, epilepsy laterality, or medication use.

Table 4. Reproductive Endocrine Function in Treated and Untreated Women with TLE and Control Subjects

	Ctrl	TLE M	TLE NM	
N	12	27	9	
Age (yr)		$29.6 \sim 6.1$	$31.2 \sim 5.8$	$30.9 \sim 6.4$

Hypothalamus

LHPF	6.0 ~ 0.7	5.8 ~ 1.6	5.8 ~ 2.1
LHPA	2.1 ~ 0.6	2.3 ~ 0.7#	3.0 ~ 1.4*#
PRLPF	3.4 ~ 1.2	3.2 ~ 1.1	3.2 ~ 0.8
PRLPA	2.6 ~ 0.9	5.2 ~ 6.9	3.0 ~ 1.8
LH/FSH	0.93 ~ 0.35	0.89 ~ 0.49	1.0 ~ 0.6

Pituitary

LH	4.7 ~ 1.5	4.8 ~ 2.2	5.3 ~ 3.4
FSH	5.2 ~ 0.9	6.1 ~ 2.1	5.3 ~ 1.3
PRL	9.2 ~ 3.2	8.8 ~ 3.9	7.3 ~ 2.5

Peripheral gland

Testo	32 ~ 11	29 ~ 14	28 ~ 15
DHEAS	189 ~ 51	94 ~ 68**##	160 ~ 65##
E2	35 ~ 6	21 ~ 7**	25 ~ 7**

TLE M or NM vs Ctrl:

* p 0.05

** p 0.01.

TLE M vs NM:

p 0.05

p 0.01.

For other abbreviations, see Table 2.

PRLPA was significantly more variable among women with TLE than among controls (4.6 ~ 6.1 vs 3.0 ~ 1.5; $p < 0.001$; see Table 2). Variability was significantly greater among women with RTLE than among women with LTLE (6.7 ~ 8.6 vs 3.0 ~ 1.8; $p < 0.001$). PRLPA values were significantly greater for treated women with RTLE (8.1 ~ 9.6) than for untreated women with RTLE (2.4 ~ 0.7; $p < 0.05$), as well as women with LTLE (treated: 2.9 ~ 1.7; $p < 0.05$; untreated: 3.5 ~ 2.3; $p < 0.10$) and controls (3.0 ~ 1.5; $p < 0.05$) (Fig 1). LH/FSH was significantly greater for women with LTLE than for women with RTLE (1.1 ~ 0.5 vs 0.65 ~ 0.35; $p < 0.01$ see Table 3), regardless of medication use (untreated 1.4 ~ 0.6 vs 0.58 ~ 0.10; $p < 0.01$; see Fig 1).

PITUITARY PARAMETERS

LH was more variable among women with TLE than among controls (4.9 ~ 2.5 vs 4.7 ~ 1.5; $p = 0.05$; see Table 2). The mean value was higher among untreated women with LTLE (7.1 ~ 3.7) than among treated women with LTLE (5.0 ~ 1.9; $p < 0.10$) and controls (4.7 ~ 1.5; $p < 0.10$), and more than twofold greater than the mean value for untreated women with RTLE (3.1 ~ 0.9; $p = N.S.$ see Fig 1).

FSH was more variable among women with TLE than among controls (5.9 ~ 2.0 vs 5.2 ~ 0.9; $p = 0.01$) (see Table 2). FSH was significantly higher for women with RTLE (6.7 ~ 2.0) than women with LTLE (5.3 ~ 1.8; $p < 0.05$; see Table 3). This lateralized difference among women with TLE was statistically significant only among treated women (7.1 ~ 2.0 vs 5.4 ~ 2.0; $p < 0.05$; see Fig 1). PRL did not show any significant finding in relation to epilepsy, epilepsy laterality, or medication use.

PERIPHERAL ENDOCRINE GLAND PARAMETERS

Testosterone levels were significantly greater for LTLE than RTLE (35 ~ 16 vs 22 ~ 9; $p < 0.01$) as they were for controls (32 ~ 11 vs 22 ~ 9; $p < 0.01$; see Table 3). There was no relationship to medication use.

Estradiol levels were significantly greater among controls than women with epilepsy (35 \pm 6 vs 22 \pm 8; $p < 0.001$; see Table 2) regardless of medication use (untreated 25 \pm 7; $p < 0.01$; treated 21 \pm 7; $p < 0.01$; see Table 4). E2 levels were significantly greater for LTLE than RTLE (25 \pm 7 vs 18 \pm 6; $p < 0.01$; see Table 3) and each was significantly less than controls (35 \pm 6; $p < 0.01$; see Table 3). Lower E2 values with medication use were attributable to the use of enzyme-inducing drugs (E2 for barbiturate, carbamazepine, phenytoin users vs controls = 14.5 \pm 4.5 vs 35.4 \pm 6.2; $p < 0.001$) as opposed to non-enzyme-inducing drugs (E2 for gabapentin, lamotrigine, valproate users vs controls = 28.3 \pm 9.4 vs 35.4 \pm 6.2; $p = \text{N.S.}$). Untreated women with TLE had substantially lower E2 levels (24.9 \pm 7.6) than controls (35.4 \pm 6.2), albeit without statistical significance ($p < 0.20$).

DHEAS values were significantly greater for controls than for women with TLE (189.2 \pm 51.1 vs 110.4 \pm 72.7; $p < 0.001$; see Table 2). DHEAS values were significantly greater for controls (189.2 \pm 51.1; $p < 0.01$) and untreated women with TLE (160.1 \pm 65.3; $p < 0.01$) than for treated women with TLE (93.8 \pm 68.2; see Table 4). Lower DHEAS values with medication use were attributable to the use of enzyme-inducing drugs (DHEAS for barbiturate, carbamazepine, phenytoin users vs controls: 49.2 \pm 37.2 vs 189.2 \pm 51.1; t test $p < 0.001$) as opposed to non-enzyme-inducing drugs (DHEAS for gabapentin, lamotrigine, valproate users = 108.5 \pm 50.7 vs 189.2 \pm 51.1; t test $p = \text{N.S.}$). Values for enzyme-inducing drug users were significantly lower than for non-enzyme-inducing drug users (49.2 \pm 37.2 vs 108.5 \pm 50.7; $p < 0.001$).

CORRELATIONAL ANALYSES

Among controls, LHPF correlated inversely with LHPA ($p = 0.04$) and PRLPF ($p = 0.006$). LHPA correlated with E2 ($p = 0.06$). Among women with epilepsy, LHPF correlated with LH ($p = 0.003$) and testosterone ($p = 0.04$). LHPA correlated significantly with PRL ($p = 0.04$).

Reproductive Endocrine Predictors of Temporolimbic Epilepsy Laterality and Medication Use

Stepwise logistic regression analysis of the data indicated that LHPF ($p = 0.014$), testosterone ($p = 0.006$), and E2 ($p = 0.025$) were significant predictors of TLE laterality with higher values being associated with left laterality. LH/FSH ratio ($p = 0.12$) may warrant mention as well, although it did not reach statistical significance. Laterality detection showed a sensitivity of 90% with a specificity of 88%. Both DHEAS ($p = 0.01$) and E2 ($p = 0.01$) were significant predictors of medication use with lower values in treated women.

Menstrual and Reproductive Endocrine Disorders: Temporolimbic Epilepsy versus Control; Left-Sided Temporolimbic Epilepsy versus Right-Sided Temporolimbic Epilepsy

Menstrual disorders were more common in women with TLE than among women in a separate control series (12/36 [33.3%] vs 14/100 [14.0%]; $2 p = 0.02$). There was, moreover, a statistically significant relationship ($p < 0.05$; Table 5) between the occurrence of particular reproductive endocrine disorders (PCOS, HA) and the laterality of interictal paroxysmal discharges. In particular, PCOS occurred in 8 out of 36 (22.2%) women with TLE as compared with 5 out of 100 (5%) in the separate control series ($2 p < 0.05$). It was more common with LTLE (7/20) than RTLE (1/16) and was more common among untreated (3/9 [33.3%]) than treated (5/27 [18.5%]) women with TLE.

Table 5. Reproductive Endocrine Disorders and Epilepsy Laterality

N	Reproductive Endocrine Function
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	PCOS	HA	Normal	
LTLE	20	7	0	13
RTLE	16	1	2	13

Chi-square = 6.13, d.f. = 2; p = 0.046. LTLE, left temporolimbic epilepsy; RTLE, right temporolimbic epilepsy; PCOS, polycystic ovarian syndrome; HA, hypothalamic amenorrhea; Normal, normal reproductive endocrine status.

Paroxysmal Electroencephalogram Discharges and Acute Reproductive Endocrine Changes

Abnormal paroxysmal EEG discharges occurred in 26 out of the 36 subjects. These consisted of unilateral temporal epileptiform discharges in 18 (10 with left and 8 with right laterality) and unilateral or bilateral slowing in 10. Epileptiform discharges were frequently accompanied by acute disruptions of LH and PRL secretion that did not occur among controls (Table 6). The most frequent pattern consisted of prolactin elevations that exceeded 2.5 times the value of the preceding nadir. This finding occurred in 15 out of the 18 women with TLE (RTLE, 7 out of 8; LTLE, 8 out of 10; TLE vs controls, 2 p = 0.01). Peak values were reached 10 to 40 minutes after the onset of EEG discharges, with a return to baseline during the hour after their cessation. Abnormally high peak levels, that is, above the control maximum, occurred in 6 out of the 8 women with RTLE and in only 2 out of the 10 women with LTLE (2 test p = 0.02). Protracted duration of discharges was often associated with a protracted elevation of the mean PRL baseline (Fig 2). In women with LTLE, 80% of abnormal PRL elevations were accompanied by a cessation of LH pulsatility for an abnormal interval, that is, greater than 104.3 minutes, which is the control mean + 2 SD value for pulse durations (see Table 6). All had a subsequent resumption of pulsatility with an abnormal elevation in mean baseline LH values, that is, nadir pulse values after paroxysmal discharges increased by greater than 27% above values that preceded the discharges, with 27% representing the normal control mean nadir + 2 SD value (see Fig 2). In contrast, PRL elevation with RTLE was accompanied by an LH pulse cessation or subsequently greater than 27% increase mean baseline LH in only 25% (LTLE vs RTLE, 2 p = 0.06; see Table 6, and Fig 2).

Table 6. Acute PRL and LH Changes following Interictal Epileptiform Discharges

	LTLE (N = 10)	RTLE (N = 8)	2 test p value
Abnormal PRL elevation (peak/nadir > 2.5)	8 (80%)	7 (75%)	NS
Abnormal PRL elevation (peak value > 15.6 ng/ml)	2 (20%)	6 (75%)	0.06
Loss of LH pulsatility (no peak for > 104.3 min)	8 (80%)	2 (25%)	0.06
Abnormal (>27%) in mean baseline LH	8 (80%)	2 (25%)	0.06

PRL, prolactin; LH, luteinizing hormone; LTLE, left-sided temporolimbic epilepsy; RTLE, right-sided temporolimbic epilepsy; NS, not significant.

Figure 2. Interictal paroxysmal electroencephalogram discharges and closely related reproductive endocrine changes in gonadotropin and prolactin secretion in women with left- and right-sided unilateral temporolimbic epilepsy. Left temporal discharges were often accompanied by abnormal suppression (> 104.3 minutes without a pulse peak) of LH pulsatility (downward black arrows) and subsequent abnormal > 27% elevation in mean baseline LH levels (brackets). Right temporal discharges were often followed by abnormally high prolactin pulse peak values and continuation of LH pulsatility (upward black arrows). LH, luteinizing hormone; PRL, prolactin; LTLE, left-sided temporolimbic epilepsy; RTLE, right-sided temporolimbic epilepsy. [Normal View 47K | Magnified View 118K]

Relationship among Interictal Paroxysmal Electroencephalogram Discharges, Reproductive Endocrine Dysfunction, and Menstrual Disorders

Menstrual disorders were more common among women with TLE who had abnormal LHPF (8/14 [57.1%] vs 4/22 [18.2%]; $p = 0.04$) and interictal epileptiform discharges (9/18 [50%] vs 3/18 [16.7%]; $p = 0.08$).

Discussion

Abstract

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Reproductive Endocrine Function Differs between Women with TLE and Normal Controls

Serum estradiol and DHEAS levels are significantly lower among the women with epilepsy. LHPF, PRLPA, FSH, and possibly LH show a greater variability among women with TLE than among controls. The finding of diminished estradiol is consistent with previous observations[25-28] and may be related to earlier perimenopause and menopause.[29][30] The reduction in DHEAS has long been recognized to be a feature of enzyme-inducing antiepileptic drug (AED) use.[31] Neurologically, DHEAS is a highly neuroexcitatory steroid that potentiates glutamatergic and blocks -aminobutyric acid-mediated conduction.[32] As such, reduction in concentrations may potentially lessen neuronal excitability and seizure tendencies. Systemically, low DHEAS values may be associated with higher low-density lipoprotein levels and higher rates of cardiovascular disease and stroke.[33] Unfavorable abnormal lipid profiles have been documented among women who take AEDs.[34][35] Estradiol and DHEA, along with its sulfated ester DHEAS, are neuroexcitatory and clinically energizing and antidepressant steroids.[36-38] The potential role of their lower levels in emotional changes, especially mood disorders that are unusually common among women with epilepsy,[39-41] remains to be established.

The finding of a greater variability of hypothalamopituitary secretion has been reported in the past[22-24] and attributed to altered cerebral modulation of the axis[7-10] as well as to AED effects.[7][11][23][25-28][31] The clinical significance rests in the potential for this alteration to reach sufficient magnitude as to disrupt ovulation, luteinization, and hence lead to the development of reproductive endocrine disorders, menstrual disorders, and infertility. There is both animal experimental[42-45] and clinical[6][9][10][25-28] evidence, including the present findings, to suggest that this process might be the case. Anovulatory cycles may also affect seizures adversely.[46-48] Specifically, the higher serum estradiol to progesterone ratios during the second half of each anovulatory cycle may have a net neuroexcitatory effect that may increase seizure frequency.[46-48]

Reproductive Endocrine Function in Women with Temporolimbic Epilepsy May Relate to Epilepsy Itself and Varies in Relation to the Laterality of Paroxysmal Temporolimbic Epileptiform Discharges

The notion that epilepsy may promote the development of reproductive endocrine dysfunction has been based on (1) the massive direct connections between the amygdala, a frequent site of involvement in adult epilepsy,[2][3] and the regions of the hypothalamus that are involved in the regulation, production, and secretion of reproductive hormones;[1][8] (2) evidence that amygdaloid stimulation affects neuronal excitability,[49-51] GnRH content,[52][53] and neuroendocrine secretion[4][22][42][54][55] in these hypothalamic regions, (3) the observation of a higher frequency of a particular reproductive endocrine disorder (PCOS) among untreated than treated women with epilepsy,[6][14] and (4) the observation of a possible lateralized asymmetry in the association between unilateral TLE and specific reproductive endocrine disorders.[10] Specifically, LTLE and R non-TLE have been associated with PCOS, whereas RTLE has been associated with HA.[10] The current findings support this impression because characteristic

features of PCOS, namely higher LHPF, LH/FSH ratios, testosterone, and DHEAS, were demonstrated with LTLE than RTLE. These lateralized findings may have their basis in (1) differences between the left and right temporolimbic-hypothalamopituitary axis in terms of hormone content,[56] and reproductive physiology,[56-58] and (2) the laterally asymmetric, ipsilaterally predominating activation of the sexually dimorphic reproductive endocrine regulatory regions of the hypothalamus by unilateral temporolimbic discharges.[51][53]

Reproductive Endocrine Function in Women with Temporolimbic Epilepsy Varies in Relation to Particular Antiepileptic Drug Use

Although both DHEAS ($p = 0.01$) and E2 ($p = 0.01$) were significant predictors of medication use, with substantially lower values in treated women, the values were significantly diminished only among enzyme-inducing (barbiturates, phenytoin, and carbamazepine) AED users and not among non-enzyme-inducing AED users (gabapentin, lamotrigine, and valproate). Some enzyme-inducing drugs have been noted in the past to decrease DHEAS[27][31][59] and estradiol levels.[25-28] Because thyroid status impacts reproductive function, it is also important to note that enzyme-inducing AED use has also been associated with abnormally low thyroxine and free thyroxine levels, often without compensatory elevation in thyrotropin.[27][59-62] In contrast, the non-enzyme-inducing AED valproate has been associated with normal DHEAS, thyroxine, and thyrotropin levels[62] but elevated serum concentrations of testosterone,[26][63-65] greater insulin resistance,[66] and the suggestion of a higher frequency of PCOS.[15][67][68] With regard to the last point, the results in the present investigation are inconclusive. Only 2 out of the 36 women with TLE were on valproate monotherapy. One had the clinical, endocrine, and ultrasound features of PCOS.

Separate and Interactional Effects between Epilepsy and Antiepileptic Drugs on Reproductive Endocrine Function

Differences in reproductive endocrine findings between women with epilepsy and control subjects may be due to epilepsy, AED use, or both. LHPF, LH/FSH, LH, and testosterone are higher in untreated women with LTLE than in untreated women with RTLE. These differences appear to be related to the epilepsy and, in particular, to laterality effects. Estradiol and DHEAS levels are lower in treated women with epilepsy, specifically in those who were taking enzyme-inducing AEDs. Both hormones, however, showed an effect of the epilepsy as well. Specifically, DHEAS was higher among untreated women with LTLE than untreated women with RTLE. Estradiol, likewise, was higher in women with LTLE than RTLE. PRLPA was more variable among women with TLE than controls. This increased variability occurred only with RTLE and, in particular, those with RTLE who were treated with AEDs. The findings of interactional effects between epilepsy and particular AEDs may need to be considered and controlled in future investigations.

Menstrual and Reproductive Endocrine Disorders Are More Common among Women with Temporolimbic Epilepsy Than among Normal Controls

Despite extensive investigation, a precise definition for normal menstrual cycle intervals has proven elusive and has ranged anywhere from the older defined ranges of 26 to 32 days to the newer ones that are as broad as 21 to 35 days.[12] The basis for extending the range is not well established. If the major medical significance of menstrual disorders is anovulation and its reproductive consequences, and, in women with epilepsy, anovulation carries the added risk of increased seizure frequency,[46][48] then the definition of menstrual disorder, especially in women with epilepsy, should be based on data relating cycle intervals to rates of ovulation. In a

recent investigation,[12] anovulatory cycles were significantly greater in proportion in women with 21- to 25- or 33- to 35-day cycles as well as in women with less than a 21- or more than a 35-day cycle intervals than in women with 26- to 32-day intervals. Serum estradiol to progesterone ratios, moreover, were significantly greater in women with cycle intervals that were less than 26 or greater than 32 days. For this reason, we retain the older definition of a normal cycle interval. In this investigation, menstrual disorders (abnormal cycle interval, oligomenorrhea, polymenorrhea, increased variability of cycle interval, or menometrorrhagia) were almost 2.5 times more common in women with TLE than among women in a separate control series (ie 12/36 [33.3%] vs 14/100 [14.0%]; $2 p = 0.02$).

Reproductive endocrine disorders were overrepresented among women with unilateral TLE. Ten women, that is, 27.8% (eight with PCOS and two with HA), were affected. This rate is over three times greater than the expected frequency in the general population of approximately 8%.[6][15][69] PCOS was the most common. It occurred in 8 out of the 36 women with unilateral TLE, that is, 22.2%. The frequency of PCOS, defined as hyperandrogenic anovulation, that is, elevated testosterone along with clinical (menstrual), endocrine, or ultrasound evidence of anovulation, was approximately 4 times greater than the 5% frequency of PCOS in our separate control group of 100 women. Although our subjects were selected for the presence of unilateral TLE, the frequency of PCOS in these women with epilepsy was similar to that found in our previous, perhaps more representative, outpatient clinic studies[6][70] and in the range of findings by others (c.f. 15). These frequencies in women with TLE are about 4-5 times greater than the 4.5% demonstrated in a population study by Knockenhauser and colleagues[69] and are clinically important because PCOS is associated with an increased risk of infertility, migraine, emotional disorders, insulin resistance, cardiovascular disease, and cancer (c.f. 15). Hypothalamic amenorrhea is thought to affect anywhere from 1 to 2% of women in the general population.[6][16] Features of hypothalamic amenorrhea were detected in 2 out of the 36 women with TLE, that is, 5.6%. This increased frequency is consistent with our previous demonstration of an overrepresentation of this disorder in women with TLE.

Lateralized Asymmetries in the Regulation of Reproductive Endocrine Function Are Associated with the Occurrence of Different Reproductive Endocrine Disorders in Women with Left and Right Temporolimbic Epilepsy

Among women with unilateral TLE, there appears to be a significant relationship between the laterality of paroxysmal epileptiform discharges and reproductive endocrine secretion at all levels of the reproductive neuroendocrine axis. Stepwise logistic regression suggested that LHPF, testosterone, and estradiol, and possibly LH/FSH ratio were significant predictors of EEG laterality, with higher values being found on the left. There was also a significant relationship between the laterality of interictal paroxysmal discharges and the occurrence of particular reproductive endocrine disorders. In particular, PCOS occurred in 8 out of 36 (22.2%) women with TLE. It was more common among untreated (3/9 [33.3%]) than treated (5/27 [18.5%]) women with TLE. It was more common with LTLE (7/20 [35%]) than RTLE (1/16 [6.25%]). These findings are particularly remarkable, because the direction of endocrine changes noted with LTLE are characteristic of PCOS and support a postulated mechanism by which disruption of temporolimbic modulation of hypothalamic neuroendocrine function might be a contributory factor.[8]

Interictal Paroxysmal Electroencephalogram Discharges Are Associated Temporally with Closely Related Reproductive Endocrine Changes in Gonadotropin and Prolactin Secretion

The possibility that epileptiform discharges may disrupt the temporolimbic modulation of hypothalamopituitary function draws support also from the close temporal relationship between paroxysmal discharges and the occurrence of abnormal changes in LH and PRL secretion. The finding of greater elevations of PRL closely following right lateral discharges and the greater frequency of LH pulse suppression followed by elevation of mean baseline LH after left lateral discharges lends support for this mechanism as well as the lateralized asymmetry of neuroendocrine control. It is noteworthy that the elevation in mean baseline LH after left temporolimbic discharges was not accompanied by any elevation in FSH. This feature may be consistent with the increased LH/FSH ratio that is associated with LTLE and is a feature of PCOS. Elevated LH/FSH has also been found by Zolovick in female rats after amygdaloid lesions.[42] Previous investigations have shown elevated LHPF[9] and LHPA[71] interictally, as well as abnormally large variability of PRL levels associated with RTLE but not LTLE.[72]

There Is a Relationship among Abnormal Interictal Paroxysmal Electroencephalogram Discharges, Reproductive Endocrine Dysfunction, and Menstrual Disorders

The findings bring together significant associations among the occurrence of (1) paroxysmal epileptiform discharges, (2) altered pulsatile secretion of gonadotropin, and (3) menstrual disorders. Specifically, TLE and paroxysmal epileptiform discharges are associated with altered LHPF. Abnormal LHPF is associated with a significantly higher proportion of menstrual disorders than normal LHPF (57.1% vs 18.2%; $p = 0.04$). Menstrual disorders are almost threefold more common (50% vs 16.7%; $p = 0.08$) among women who were recorded to have paroxysmal epileptiform interictal activity.

In summary, the findings indicate that reproductive endocrine function differs between women with epilepsy and normal controls. Significant differences exist at all levels of the reproductive neuroendocrine axis. Differences show significant relationships to epilepsy itself, epilepsy laterality, and particular AEDs. Menstrual disorders are more common among women with interictal discharges as well as women with abnormal hormonal findings.

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