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# Relationship of sexual dysfunction to epilepsy laterality and reproductive hormone levels in women☆

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**Abstract**

Sexual dysfunction has been reported to be common among women with epilepsy. Controlled studies, quantitative data, and investigations of potentially contributory factors, however, have been few. The purpose of this investigation was to determine if (1) sexual dysfunction is unusually common among women with partial seizures of temporal lobe origin (TLE), and (2) sexual dysfunction varies in relation to the laterality of EEG epileptiform discharges, antiepileptic drug use, and serum gonadal steroid levels. This controlled prospective investigation used a quantitative sexual rating scale and reproductive hormone measures to compare sexual dysfunction in women with left and right unilateral temporolimbic epilepsy and controls. Sexual dysfunction scores were significantly higher in women with TLE, and sexual dysfunction affected substantially more women with epilepsy than controls. Women with right-sided foci were affected more than women with left-sided foci. There was a significant inverse correlation between sexual dysfunction and bioactive testosterone levels in women with epilepsy as well as in controls. Serum estradiol was lower in women with TLE but did not correlate significantly with overall sexual dysfunction. The findings suggest that sexual dysfunction is significantly more common in women with right-sided epileptiform discharges than in controls and is inversely correlated with bioactive testosterone levels. The value of hormonal replacement or supplementation remains to be explored.


*Keywords:* Epilepsy; Hormones; Reproductive; Endocrine; Laterality; Sex

## 1. Introduction

The brain regulates sexual behavior by neural and neuroendocrine mechanisms [1–5]. The temporolimbic system, in particular, has been implicated in both of these mechanisms [1–5]. Bilateral damage to the system, especially the amygdala, can result clinically, as well as in animal models, in behavioral changes that feature hypersexuality (Kluver–Bucy syndrome) [6]. Temporolimbic epilepsy (TLE) can result in altered, especially diminished, sexuality in both animals and humans [7–17]. There are reports, moreover, to suggest that hypersexuality may be more prominent with right than with left temporolimbic foci [18,19].

Reproductive steroids modulate sexual interest and behavior [20–23]. Androgens play an important role in sexual interest in women as well as in men, while estrogens are important in sexual response in women [20–23]. The brain controls reproductive endocrine secretion primarily through the hypothalamic regulation of pituitary secretion [1,2]. 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 [1,2]. Disruption of temporolimbic activity by epileptiform discharges may lead to chronically altered hypothalamopituitary regulation of gonadal secretion and promote the development of reproductive endocrine disorders [1,24–28]. Reproductive

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endocrine disorders are unusually common among women with TLE [13,27]. The observation 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 relationship [29].

The main objective of the overall investigation was to determine if unilateral TLE is associated with changes in sexual function, reproductive function, and reproductive endocrine secretion, and to assess the influence of EEG laterality, antiepileptic drugs (AEDs), and reproductive hormones on sexual and reproductive function in women with TLE. In this report, we present findings regarding sexual function. This part of the investigation assessed whether (1) sexual dysfunction is unusually common among women with unilateral TLE, and (2) sexual dysfunction varies in relation to the laterality of paroxysmal temporolimbic epileptiform discharges, AED use, and reproductive steroid levels.

## 2. Patients and methods

### 2.1. Research design

This investigation compared sexual, reproductive, and reproductive endocrine function between women with unilateral left and right TLE and normal controls. Epilepsy-related variables under consideration included (1) laterality of the epileptic focus and (2) AED use. Sexual interest and function during the preceding week were measured using the Arizona Sexual Experience Scale (ASEX) questionnaire [30]. This is a standardized, validated, reliable five-item rating scale that quantifies sexual interest, arousal, response, and satisfaction. Each question is scored out of 6. Higher scores reflect greater sexual dysfunction. A total score between 5 and 30 is determined. Scores that exceeded the control mean plus two standard deviation value were used to categorize sexual dysfunction. Reproductive function was assessed by characterization of menstrual cycle intervals and menses, as well as documentation of hirsutism and galactorrhea. 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 some aspects of pulsatile gonadotropin and prolactin secretion, in particular luteinizing (LH) hormone and prolactin (PRL) pulse frequency (PF) and pulse amplitude (PA). Pituitary function was assessed by serum LH, FSH, and PRL levels, as well as serum LH/FSH ratio. Peripheral gland measures were serum testosterone (T), bioactive testosterone (BAT), estradiol (E2), and dehydroepiandrosterone sulfate (DHEAS). Testosterone was measured in its bioactive form because normally, a high percentage, approximately 45%, is inactivated by tight binding to sex hormone-binding globulin (SHBG), and this percentage is elevated further by enzyme-inducing AED use [31]. Only 10% of estradiol, in contrast, is bound to SHBG [31].

### 2.2. Patients

The experimental group was recruited from the outpatient neurology practice of our institution and consisted of 36 women between the ages of 18 and 40 years who were recruited on the basis of having clinical and EEG evidence that suggested unilateral temporolimbic epilepsy. The women were divided into four groups on the basis of EEG laterality and AED use: (1) LTLE-treated, (2) LTLE-untreated, (3) RTLE-treated, and (4) RTLE-untreated. All had at least monthly complex partial seizures and EEG documented unilateral left (LTLE—20)- or right (RTLE—16)-sided temporal lobe interictal epileptiform discharges. EEG documentation was obtained in the preceding 3 months in all cases. The majority (24/36) 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 (SPECT). The epileptic subjects included 27 AED-treated (carbamazepine, 8; phenytoin, 8; valproate, 2; gabapentin, 2; polytherapy, 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. All treated women had at least one current serum AED level in the therapeutic range at the time of investigation. No subject had a known clinical seizure during the 24 h prior to 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.

No subject took hormones, major tranquilizers, or antidepressants during the 3 months prior to testing.

### 2.3. Methods

All women were tested during the early to midfollicular phase (Days 3–7) of the menstrual cycle, with the majority being tested on Day 4. Following a duly authorized consent procedure, the women were admitted to the Clinical Research Center during the afternoon before the day of testing. The salient features of the history were reviewed. Reproductive, sexual (ASEX), and emotional [Profile of Mood States (POMS)] [32]

rating scales were completed. EEG recording electrodes were attached to the scalp and bandaged in place. Beginning at 8:00 AM on the next day, 5-cc blood samples were drawn at 10-minute intervals for 8 hours via 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 EEGs were read by D.L.S. without knowledge of questionnaire scores or endocrine data. The schedule and content of meals were standardized for all subjects.

### 2.4. Hormone analysis

Blood samples were centrifuged immediately, the serum was separated, and the samples were frozen at −20 °C until hormonal assays were performed. Commercially available kits were used to assay the hormones by standardized fluoroimmunoassay for gonadotropins and prolactin (Delfia) and by radioimmunoassay for steroids (Diagnostic Products Corporation). FSH, LH, and PRL were assayed with the manual time-resolved fluorometry method. LH and PRL samples were assayed in duplicate for subsequent pulse analsysis. The Delfia test kits were purchased from EG&G Wallac. Delfia assays were based on the time-resolved fluorometry and the measurement of lanthanide chelate fluorophores. The Bio-Rad Lyphochek multileveled Immunoassay Plus Controls were used for these tests. The control ranges were provided by the company. Two sets of controls were used within each assay run. One set was placed at the beginning and another at the end to monitor the drift, and an extra set was placed in the middle for large runs. A tighter in-house range was calculated after 25 sets of data were collected from the same lot number. The run was accepted only if the controls were within the two standard deviations from the mean. All standards, controls, and the unknowns were run in duplicate and data with <10% coefficient of variance were considered acceptable. Total testosterone, DHEAS, estradiol, and progesterone were assayed with the radioimmunoassay method. Bioactive testosterone, i.e., non-sex-hormone-binding globulin-bound testosterone, was determined after precipitation and absorption of SHBG-bound testosterone using ammonium sulfate. The test kits were purchased from Diagnostic Products Corporation. The radioactive isotope $^{125}$I was used as the label. The assays were measured by using the Isomedic gamma counter from ICN Biomedicals. Diagnostic Products Corporation's CON6 Multivalent Control Module was used for the radioimmunoassays. The same quality control criteria were applied using the Lyphocheks mentioned above. Intraassay and interassay variability was determined for all assays and limited to 5 and 10%, respectively.

### 2.5. Statistical analysis

Sexual function scores were compared between women with TLE and controls using the Student $t$ test. The proportion of women with TLE who had sexual dysfunction, i.e., scores that were more than two standard deviations above the normal mean, was compared with that of normal controls using the $\chi^2$ test. Comparisons of sexual function were also carried out using these statistical tests with consideration of TLE laterality, AED use, and the existence of reproductive disorders and reproductive endocrine disorders as predetermined variables. The relationship of sexual function scores to specific hormone levels was assessed using Pearson correlation analysis. The $P$ values were evaluated for two-tail outcome.

## 3. Results

### 3.1. Demographic data

The four groups of women with TLE and the control group did not differ significantly in age or marital rate (Table 1). The four groups of women with TLE did not differ significantly in their duration of epilepsy, monthly seizure frequency, or proportion with a history of secondary generalized seizures. Twenty-six of the women with epilepsy had paroxysmal discharges, 18 with epileptiform discharges and 8 with paroxysmal slowing. All were unilateral and coincided with the laterality that was designated at the time of enrollment. Twenty-five percent

Table 1
Demographics of controls and women with epilepsy[a]

| | Controls ($N = 12$) | L TLE M ($N = 15$) | L TLE NM ($N = 5$) | R TLE M ($N = 12$) | R TLE NM ($N = 4$) |
|---|---|---|---|---|---|
| Age (years) | 29.6 ± 6.1 | 30.9 ± 5.8 | 28.8 ± 7.5 | 32.9 ± 5.4 | 29.8 ± 7.2 |
| Duration of epilepsy (years) | — | 8.2 ± 6.4 | 5.4 ± 4.8 | 7.7 ± 5.4 | 6.2 ± 4.1 |
| Seizure frequency/month | — | 7.2 ± 4.8 | 5.2 ± 4.5 | 6.8 ± 5.4 | 4.6 ± 4.4 |
| Number (%) with SGMS | — | 8 (53%) | 2 (40%) | 7 (58%) | 2 (50%) |
| Married | 6 | 7 | 3 | 5 | 2 |

[a] Values are means ± SD. TLE, temporolimbic epilepsy; L/R, left/right laterality; M/NM, medicated/nonmedicated; SGMS, history of secondary generalized motor seizures.

(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.

### 3.2. Sexual dysfunction data

ASEX scores were significantly higher, i.e., worse, among women with TLE than among controls regardless of laterality (TLE vs control: 17.5 ± 5.5 vs 11.9 ± 4.0, $P < 0.01$; LTLE vs control: 15.6 ± 3.7 vs 11.9 ± 4.0, $P = 0.01$; RTLE vs control: 19.9 ± 6.4 vs 11.9 ± 4.0, $P < 0.001$) (Table 2). Women with RTLE had scores that were significantly higher than those of women with LTLE (19.9 ± 6.4 vs 15.6 ± 3.7, $P = 0.05$). There was no significant difference between treated and untreated women with epilepsy overall (treated vs untreated: 17.9 ± 5.6 vs 16.2 ± 4.8, $P$ = NS) or considered separately for women with LTLE (16.1 ± 3.8 vs 14.0 ± 3.5, $P$ = NS) and RTLE (20.3 ± 6.9 vs 19.0 ± 5.2, $P$ = NS). When the data were broken down by both laterality and AED use, only the untreated women with LTLE showed no significant difference from controls. As a group, they had the best ASEX scores among women with TLE. The other three groups had significantly worse ASEX scores than controls.

Abnormally high ASEX scores (mean + 2 SD = 19.9) occurred in a higher proportion of women with TLE than among controls (38.9% vs 8.3%, $P = 0.10$), especially in women with RTLE (RTLE: 50.0% vs 8.3%, $P = 0.05$; LTLE: 30.0% vs 8.3%, $P$ = NS) (Table 2). There was no significant effect of treatment (treated vs untreated: 40.7% vs 33.3%, $P$ = NS).

Among controls, there was a significant inverse correlation between serum bioactive testosterone and ASEX scores ($r = -0.57, P = 0.05$). There was also a trend toward a significant inverse correlation for estradiol ($r = -0.49, P < 0.10$). Among women with TLE, ASEX scores showed a significant inverse correlation with serum BAT ($r = -0.33, P = 0.03$) (Fig. 1) but not E2 ($r = -0.19$, $P$ = NS) levels. A substantial number of women with TLE had abnormal gonadal steroid levels. Among the 20 women with LTLE, none had abnormally low BAT levels (normal range: 6.3–22.3 ng/dl) and 7 (35%) had abnormally high levels. Among the 16 women with RTLE, 3 (18.8%) had abnormally low BAT and 1 (6.3%) had an elevated level. Six of the women with

Table 2
ASEX scores and serum reproductive steroid levels in controls and women with epilepsy[a]

| | Ctrl | TLE | L TLE | R TLE | L TLE M | L TLE NM | R TLE M | R TLE NM |
|---|---|---|---|---|---|---|---|---|
| ASEX score | 11.9 ± 4.0 | 17.5 ± 5.5[c] | 15.6 ± 3.7[c,e] | 19.9 ± 6.4[c,e] | 16.1 ± 3.8[c] | 14.0 ± 3.5 | 20.3 ± 6.9[c] | 19.0 ± 5.2[c] |
| Abnormal | 1 (8.3%) | 14 (38.9%) | 6 (30.0%) | 8 (50.0%) | 5 (33.3%) | 1 (20.0%) | 6 (50.0%) | 2 (50.0%) |
| BAT (ng/dl) | 14.3 ± 4.0 | 12.1 ± 5.8 | 14.5 ± 6.2[f] | 9.1 ± 3.5[b,f] | 13.8 ± 5.9[d] | 16.4 ± 7.4[e] | 9.3 ± 3.9[b,d] | 8.3 ± 2.1[b,e] |
| E2 (pg/ml) | 35 ± 6 | 22 ± 8[c] | 25 ± 7[c,f] | 18 ± 6[c,d] | 24 ± 8[c,d] | 28 ± 5[b,d] | 18 ± 5[c,d] | 21 ± 9[c,d] |

[a] BAT - serum bioactive testosterone level; E2 - serum estradiol level.
[b] $P \leqslant 0.05$; [c] $P \leqslant 0.01$ for comparison with control values.
[d] $P \leqslant 0.10$; [e] $P \leqslant 0.05$; [f] $P \leqslant 0.01$ for comparison of left versus right TLE.

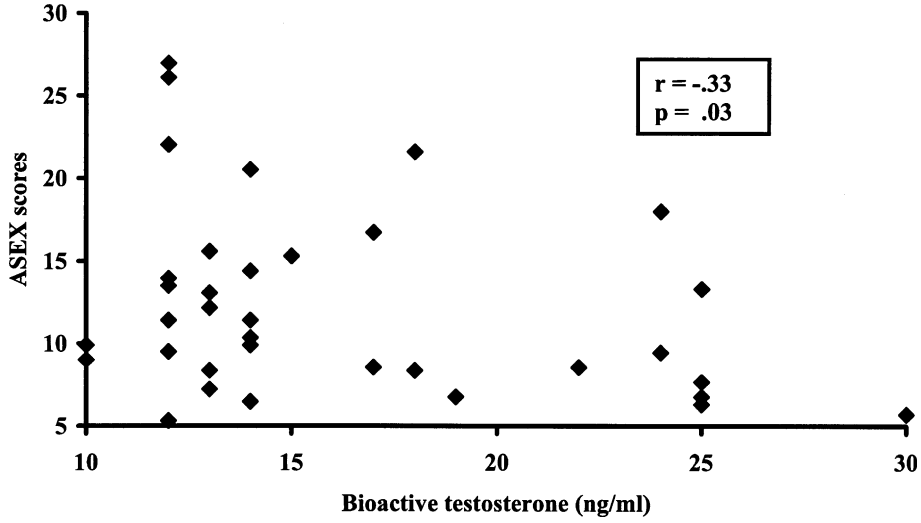


Fig. 1. ASEX scores among women with epilepsy show a statistically significant inverse correlation with serum bioactive testosterone levels ($r = -0.33, P = 0.03$).

LTLE (30%) and 9 of the women with RTLE (56.3%) had low E2 levels (normal range: 23–47 pg/ml).

## 4. Discussion

The ASEX score findings in this investigation support the notion that sexual dysfunction is common among women with TLE [7–13]. While the majority (61.1%) of women with TLE had normal-range ASEX scores, a substantial proportion (38.9%) fell above the control mean + 2 SD score of 19.9 to merit the designation of having sexual dysfunction. The mean control ($11.9 \pm 4.0$) and 2 SD cutoff (19.9) values in this investigation are comparable to the values found in the investigation that verified the validity of this scale for assessment (mean: $13.5 \pm 3.9$, cutoff: 21.3) [30]. Sexual function scores were significantly worse among women with epilepsy ($17.5 \pm 5.5$) than among controls ($11.9 \pm 4.0$), and the range of ASEX scores among women with TLE extended well above those of the control group (10–30 vs 5–20). Sexual function scores were significantly worse with RTLE ($19.9 \pm 6.4$) than LTLE ($15.6 \pm 3.7$), and only the women with RTLE (50.0%), not LTLE (30.0%), had a significantly increased incidence of sexual dysfunction as compared with controls (8.3%). The occurrence of sexual dysfunction was 22.2% greater (40.7% vs 33.3%) among AED users. The relationship of AED use to ASEX scores, however, did not show any statistical significance. Significant inverse correlations are demonstrated between ASEX scores and serum bioactive testosterone, but not estradiol, among both controls and women with epilepsy. Serum estradiol did show a trend ($p < 0.10$) toward an association with overall ASEX scores in controls. Among women with TLE, there was no such finding. A trend toward an association was found with two of the five questions dealing with vaginal lubrication and orgasm but not with the three questions dealing with sexual interest, arousal, and satisfaction.

Seizure characteristics, EEG laterality, AED use, reproductive hormone levels, and psychosocial stress have been implicated as potentially contributory factors to sexual dysfunction [15]. Temporolimbic epilepsy has been reported to be associated with sexual dysfunction more often than primary generalized epilepsy [9–12]. The nature of sexual dysfunction may differ between localization-related epilepsy and primary generalized epilepsy [15]. Although sexual arousal may be diminished with both types, women with localization-related epilepsy may experience significantly more sexual anxiety, dyspareunia, vaginismus, arousal insufficiency, and sexual dissatisfaction, whereas women with primary generalized epilepsy experienced more anorgasmia and sexual dissatisfaction [15]. Although better seizure control has been associated with better sexual function following temporal lobectomy [10,11,33], sexual symptoms were not associated with seizure frequency in the Morrell and Guldner study [15]. While the number of subjects with epilepsy in the present study is quite small to base a firm negative conclusion ($N = 36$), we find no statistically significant evidence for a relationship between sexual function and seizure frequency.

The demonstration in this investigation of a relationship between sexual dysfunction and the laterality of epileptiform discharges in women with unilateral TLE, specifically that sexual dysfunction is more common among individuals with RTLE, is in keeping with some [18,19] but not all [34] past investigations and supports a biological brain-related mechanism. There is increasing evidence to support the existence of lateralized brain asymmetries in the regulation of neuroendocrine, reproductive, and sexual functions. There is 50–100% more GnRH content in the right ventromedial hypothalamus than in the left [5] in the female rat. Unilateral ovariectomy is associated with an ipsilateral hypothalamic decrease in GnRH, whereas bilateral ovariectomy is associated with a right-sided increase in GnRH [5]. Right-sided amygdalectomy is associated with more anovulatory cycles than left [35]. The instillation of estradiol into the left ventromedial hypothalamus of a neonatal genetically female rat results in defeminization of adult sexual behavior, whereas instillation into the right ventromedial hypothalamus results in masculinized behavior [36]. The hypothalamic, pituitary, and gonadal hormonal secretory patterns of PCOS occur more commonly with LTLE, while those of HA occur more commonly with RTLE [13,26,29]. The finding of more sexual dysfunction with RTLE may reflect a lateralized asymmetry in the temporolimbic or hypothalamic representation of sexual function, especially since unilateral temporolimbic discharges preferentially influence the ipsilateral sexually dimorphic regions of the hypothalamus that are involved in sexual behavior and reproductive function [37,38]. The finding, moreover, may also reflect the significantly lower levels of BAT and E2 levels in women with RTLE. They are unlikely to be explained by emotional factors alone such as anxiety and depression since scores on these POMS subscales were actually higher with LTLE than RTLE.

The absence of any demonstrable significant effect of AED use on sexual function is surprising. Enzyme-inducing drugs are known to decrease serum bioactive testosterone levels [39], and bioactive testosterone is thought to contribute to the level of sexual interest [20–23], a notion that is supported by the present findings. Most of the non-enzyme-inducing AEDs (gabapentin, benzodiazepines, valproate) have potent GABAergic effects. GABA has substantial, regionally specific, complex effects on sexual function in animal studies [40,41]. Nevertheless, the proportions of women with abnormally high ASEX scores in this investigation are

similar among women on enzyme-inducing AEDs (8/20, 40.0%), non-enzyme-inducing AEDs (3/8, 37.5%), and no medications (3/9, 33.3%). The numbers of subjects in each treatment group, however, are small and it is still possible that comparisons of various individual AEDs using larger sample sizes may reveal differences.

The findings show a statistically significant correlation between sexual function scores and serum BAT levels. This finding in both women with epilepsy and controls supports a suspected role for testosterone in sexual function, presumably in interest or libido [20–23], in women as well as in men. Significantly lower estradiol levels may also be contributory, although a trend toward a correlation was demonstrated only in controls. These findings differ from a past investigation of this relationship in which no association was apparent between free testosterone and sexual function using different measures of biologically active testosterone (free testosterone) and sexual function (Sexual Experience Scale) [16].

By way of therapeutic intervention, the potential role of better seizure control needs to be investigated further to determine if it alone might be sufficient or whether removal of the epileptic temporolimbic substrate is also necessary to benefit sexual function. Seizure frequency was not clearly a factor in this or a previous investigation [15]. While temporal lobectomy may be associated with improved sexual function in about 20%, there are also data to suggest that worsening of function may occur in about 10% [33]. A role for testosterone replacement or supplement is suggested by the significant correlation between serum BAT levels and sexual function. The low correlation coefficient, however, suggests that BAT level may represent just one of multiple factors that contribute to the level of sexual function. Nevertheless, it does represent a factor that can be readily addressed and monitored. While only 3 of the 14 women with TLE who had sexual dysfunction were found to have abnormally low BAT levels (21.4%), the correlation between BAT levels and sexual function raises the possibility that higher levels of BAT may be required for normal sexual function in the setting of temporolimbic dysfunction in epilepsy. There is precedent to suggest that the temporolimbic substrate in animal models of epilepsy may have diminished sensitivity to reproductive steroid effects [42]. There is also clinical evidence to suggest that altered temporolimbic substrate, especially in association with paroxysmal epileptiform discharges, may be associated with altered hormonal responsivity [43–45].

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