

Psychoneuroendocrine Aspects of Temporolimbic Epilepsy

Part II: Epilepsy and Reproductive Steroids

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Reproductive dysfunction is unusually common among men and women with epilepsy. Reproductive endocrine disorders are also common and may be causal. The association between particular reproductive endocrine disorders and the laterality and focality of epileptiform discharges suggests an etiologic role for epilepsy. Gonadal steroids are neuroactive and influence seizure occurrence: estrogen is epileptogenic whereas progesterone has antiseizure effects. Fluctuations in the absolute and relative serum levels of these hormones may play a critical role in establishing three distinct patterns of catamenial epilepsy: 1) perimenstrual and 2) preovulatory in women with ovulatory cycles, and 3) entire luteal phase of the cycle in women with anovulatory cycles. Treatment with progesterone reduces seizure frequency by more than half. In men, testosterone effects may depend on the relative concentrations of two major testosterone metabolites that exert opposing influences on neuronal excitability: estrogen potentiates whereas dihydrotestosterone inhibits NMDA-mediated conductance. Combined therapy using an aromatase inhibitor along with testosterone improves sexual function and may reduce seizures in men with epilepsy.

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EFFECTS OF EPILEPSY ON HORMONES

Reproductive and Sexual Disorders Associated With Epilepsy

Reproductive dysfunction is unusually common among individuals who have epilepsy.¹ Some observations suggest that it is more common with temporolimbic epilepsy (TLE) than with generalized or focal motor seizure disorders.¹ Physiological sexual response is diminished in both men and women compared with control subjects.² Studies that deal exclusively or predominantly with women who have TLE reveal that 14–20% have amenorrhea and

that more than 50% overall have some form of menstrual dysfunction.^{3–6} One-third of cycles are anovulatory compared with 8% among control subjects.⁷ Fertility is reduced to 69–80% of the expected number of offspring.^{8,9} Investigations of men who have TLE show that 49–71% have diminished potency or sexual interest.^{10–16} The possible contribution of reproductive endocrine disorders is raised by considerable evidence of gonadal steroid, gonadotropin, and prolactin abnormalities among women and men with epilepsy.¹⁷ Some of these investigations are particularly relevant because they specifically demonstrate associations between hormonal abnormalities and sexual or reproductive dysfunction.^{4,18,19}

Evidence suggests that disorders with paroxysmal EEG findings are overrepresented among women and men with reproductive disorders. Sharf and colleagues²⁰ found that 56.5% of women with anovulatory cycles or amenorrhea, mostly in the setting of polycystic ovarian syndrome (PCO), had EEG abnormalities, including some with focal

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paroxysmal epileptiform discharges. Treatment with the antiestrogenic agent clomiphene restored EEG findings to normal in 54%. There was, moreover, an association between normalization of the EEG and the occurrence of ovulation and pregnancy. EEG abnormalities may also be more common among hyposexual men with associated reproductive endocrine abnormalities.²¹

Reproductive Endocrine Disorders Associated With Epilepsy

Reproductive endocrine disorders are significantly more common among women and men with TLE than in the general population.^{4,16,22} TLE promotes the development of reproductive endocrine disorders by neuroendocrine mechanisms, specifically the disruption of the normal limbic modulation of the hypothalamic regulation of pituitary secretion, and possibly by neural mechanisms (i.e., by alteration of the neural influences of limbic structures on the gonads).^{4,16,17,23-25} Among women with TLE, PCO and hypogonadotropic hypogonadism (HH), also known as hypothalamic amenorrhea, are significantly and notably overrepresented;⁴ men tend to have hypogonadotropic hypogonadism, hypergonadotropic hypogonadism (gonadal failure), or functional hyperprolactinemia.¹⁶ Among the women, PCO is significantly associated with left-sided temporal epileptogenic foci; HH, with right.^{4,24} Hyposexuality tends to occur with right-sided foci in the setting of HH (i.e., with low gonadotropin levels).⁴ It is unusual with PCO. In PCO, hyposexuality occurs intermittently when there is concomitant depression. Depression is a frequent associate of PCO, occurring in up to 75% of cases; it tends to respond to treatment of the PCO.²⁶ Hyposexual men with TLE also have a predominance of right-sided foci^{25,27} and have lower serum levels of biologically active testosterone than sexually asymptomatic counterparts.^{16,19,25,28,29} Diminished levels of biologically active testosterone have been attributed to three factors: 1) increased amounts of sex hormone binding globulin synthesis induced by antiepileptic medications;³⁰ 2) increased negative feedback on the hypothalamopituitary axis by antiepileptic medication-induced elevations in serum estradiol;³¹ and 3) altered patterns of hypothalamic gonadotropin-releasing hormone secretion induced by temporal lobe epileptiform discharges.²⁵

HORMONAL EFFECTS ON SEIZURES

Reproductive Steroid Effects

Considerable animal experimental and clinical evidence suggests that gonadal steroids influence the occur-

rence of seizures.^{32,33} The reproductive endocrine environment of a woman with epilepsy can undergo physiological, pathological, and pharmacological changes. Menarche,^{34,35} menstruation,^{36,37} pregnancy,^{38,39} and the process of menopause^{35,40} can be associated with altered seizure frequency. Reproductive endocrine disorders are overrepresented among women with epilepsy.^{4,41} The anovulatory and inadequate luteal phase cycles associated with them often exacerbate seizures.^{42,43} Oral contraceptives⁴⁴ and menopausal hormonal replacement⁴⁰ can exacerbate or ameliorate seizures, depending on the particular circumstances of the treatment. A knowledge of some interactions among hormones, epilepsy, and antiepileptic medications, therefore, may provide the clinician with a more comprehensive basis for the effective treatment of women with epilepsy and with related psychiatric disorders.

In many experimental animal models, estrogen lowers the thresholds of seizures induced by electroshock, kindling, pentylentetrazol, kainic acid, ethyl chloride, and other agents and procedures.^{45,46-49} In fact, the topical brain application or intravenous systemic administration of estradiol in rabbits produces a significant increase in spontaneous electrically recorded paroxysmal spike discharges.^{47,50} The increase is more dramatic in animals with pre-existent cortical lesions.⁵¹ Progesterone, on the other hand, lessens spontaneous and induced epileptiform discharges.^{45,46,48,52-54} Testosterone effects are more variable but generally tend to raise electroshock threshold, whereas orchietomy lowers it.³³

Hormones also influence human electrical brainwave activity and epilepsy. Logothetis and associates⁵⁵ showed that intravenously administered conjugated estrogen clearly activated epileptiform discharges in 11 of 16 women and was associated with clinical seizures in 4. Backstrom and coworkers⁵² found that intravenous infusion of progesterone, sufficient to produce luteal phase serum levels, was associated with a significant decrease in interictal spike frequency in 4 of 7 women with partial seizures. Testosterone therapy in epilepsy appears to be beneficial for seizure control only if used with an aromatase inhibitor, which inhibits its conversion to estrogen.⁵⁶

Catamenial Epilepsy

Catamenial epilepsy refers to seizure exacerbation in relation to the menstrual cycle.⁵⁷ Three patterns exist (Figure 1).^{57,58} About 70% of women with epilepsy may have an increase in seizures during the 3 days prior to menstruation and the first 3 days of menstruation (Pattern 1).⁵⁷

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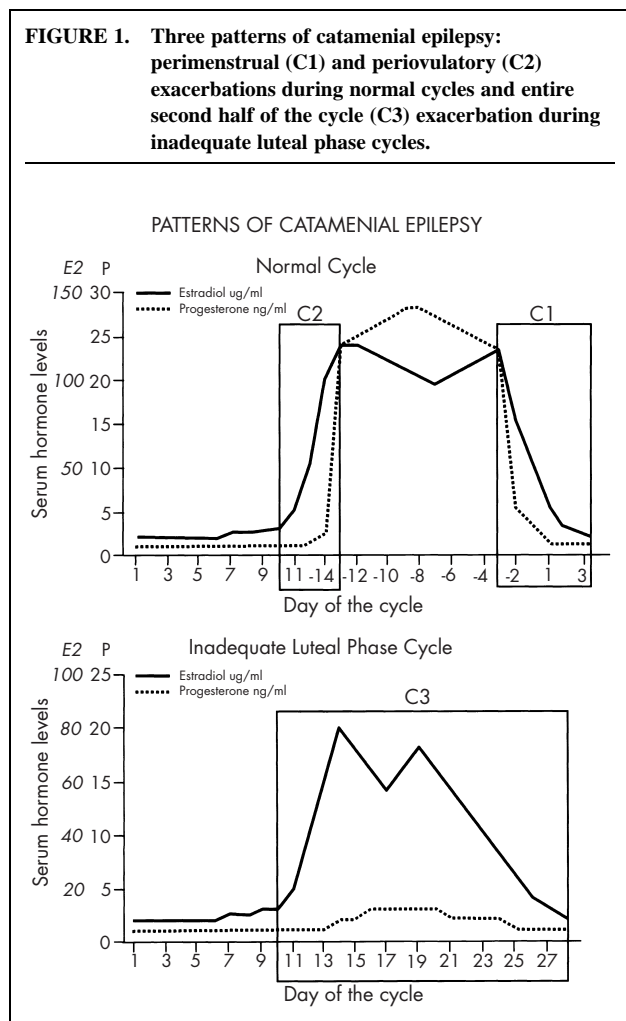
More than one-third of women with epilepsy experience a twofold or greater perimenstrual increase in average daily seizure frequency.⁵⁷ A predilection for seizure exacerbation may also occur near the middle of the cycle, between Day 10 and the day after ovulation (Pattern 2). The onset of menstruation is the reference point for Day 1. Pattern 3 is more difficult to discern; seizures are frequent between Day 10 of one cycle and Day 3 of the next, relative to the interval between Day 4 and Day 9.

Physiological endocrine secretion during the menstrual cycle influences the occurrence of seizures. In ovulatory cycles, seizure frequency shows a statistically significant positive correlation with the serum estradiol/progesterone ratio.⁵⁹ This ratio is highest during the days prior to ovulation and menstruation and is lowest during the early- and mid-luteal phase.⁵⁹ The premenstrual exacerbation of seizures has been attributed to the withdrawal

of the antiseizure effects of progesterone.³⁶ Mid-cycle exacerbations may be due to the preovulatory surge of estrogen unaccompanied by any rise in progesterone until ovulation occurs.⁵⁹ Seizures are least common during the mid-luteal phase when progesterone levels are highest.^{43,44}

Inadequate luteal phase refers to less than normal progesterone secretion during the second half of the cycle, regardless of whether ovulation does or does not occur.⁶⁰⁻⁶² It can be documented by one or preferably more findings of the following: a failure of the basal body temperature to rise by 0.7 degrees Fahrenheit for at least 10 days during the second half of the menstrual cycle; a serum progesterone level of less than 5.0 ng/ml during the mid-luteal phase, generally measured between Days 20 and 22 of a 28-day cycle; and a biopsy that shows underdeveloped secretory endometrium 8-10 days after ovulation. Serum estradiol/progesterone ratios and seizure frequencies tend to be higher than in normal ovulatory cycles during the second half of these cycles^{43,44} and seizure exacerbation may extend from Day 10 of one cycle to Day 3 of the next cycle.⁴³

The reproductive endocrine disorders associated with TLE are characterized by inadequate luteal phase cycles.⁴ As noted above, such cycles expose temporal lobe limbic structures to a continuous estrogen effect without the normal luteal phase elevations of progesterone and thereby tend to heighten interictal epileptiform activity.



HORMONAL THERAPY OF EPILEPSY IN WOMEN

Progesterone Therapy

Natural progesterone therapy benefits some women with catamenial epilepsy.⁵³ In one investigation of women who had inadequate luteal phase cycles with catamenial exacerbation of intractable complex partial seizures, 6 of 8 women experienced improved seizure control with a 68% decline in average monthly seizure frequency over 3 months for the whole group.⁵³ In a subsequent similar investigation of 25 women, 19 (72%) experienced fewer seizures with an overall average monthly decline of 54% for complex partial and 58% for secondary generalized seizures over 3 months.⁶³

Several mechanisms have been postulated to explain the sedative, hypnotic, anesthetic, and antiseizure properties of progesterone that were first described by Hans Selye.⁶⁴

Seizure activity depends on increased oxygen and glucose metabolism by the brain,^{65,66} whereas anesthesia is associated with decreased oxygen and glucose metabo-

lism.⁶⁷ Progesterone crosses the blood-brain barrier and is concentrated in the brainstem, limbic system, and cerebral cortex of the female monkey.⁶⁸ Cerebrospinal fluid concentrations of progesterone correlate directly with plasma levels in humans.⁶⁸ Progesterone decreases oxygen utilization by neurons in brain slices.⁶⁷ This effect may explain the antiseizure as well as anesthetic properties of progesterone.

Landgren et al.⁵⁴ have raised the possibility that progesterone may act directly at a cortical level. This was based on their observation in the cat that the local application of progesterone to the cortical surface inhibited the electrical discharges from a penicillin focus.

Backstrom and coworkers⁵² described a delay of 1–2 hours in the antiseizure effect of intravenously administered progesterone on the epileptic discharge frequency in women with partial epilepsy. They considered this feature to be consistent with the possibility that progesterone may act through metabolites that have been established to have marked central nervous system depressant effects.

One progesterone metabolite, allopregnanolone (3-hydroxy-5-dihydroprogesterone), is a potent barbiturate-like ligand of the GABA receptor-chloride ion channel complex, and it potentiates the inhibitory actions of GABA in cultured rat hippocampal neurons.⁶⁹

Antiseizure medication serum levels decrease premenstrually in epileptic women, especially in those with perimenstrual seizures.^{70,71} Antiseizure medications and reproductive steroid hormones are degraded by the same hepatic microsomal enzyme system.⁷⁰ The premenstrual decrease in reproductive steroid serum levels, therefore, may permit increased hepatic metabolism of antiseizure medications⁷⁰ and result in elevated seizure frequency. The premenstrual supplementation of progesterone, in contrast, may reduce this effect. This mechanism, however, is unlikely to account for all of the antiseizure effects of progesterone since two of the six women in our first series improved even though they did not receive concomitant antiseizure medications.⁵³

Phyllis⁷² presented data that suggest that progesterone may potentiate the effects of the endogenous anticonvulsant adenosine.

Progesterone binds specific cytoplasmic receptors not only to produce its own characteristic effects but also to lower estrogen receptor numbers and thereby antagonize estrogen actions on neuronal plasticity and excitability.⁷³

Another feature of progesterone therapy that may help to elucidate its mechanism of action and also serve as a practical note is illustrated by the observation that some

hormonally treated epileptic women do well each month during the course of therapy but may experience their usual premenstrual exacerbation of seizures after the discontinuation of progesterone. This effect is eliminated, or markedly lessened, when these patients gradually taper the progesterone over 3 or 4 days, rather than discontinue it abruptly.

Synthetic progestin therapy has also benefited some women with epilepsy.^{74,75} Parenteral depomedroxyprogesterone significantly lessens seizure frequency when it is given in sufficient dosage to induce amenorrhea.^{74,75} A regimen of approximately 120–150 mg, given intramuscularly every 6–12 weeks, generally achieves this goal.⁷⁴ Side effects include those encountered with natural progesterone. Depot administration, however, is also commonly associated with hot flashes, irregular breakthrough vaginal bleeding, and a lengthy delay of 6–12 months in the return of regular ovulatory cycles.⁷⁴ Long-term hypoestrogenic effects on bone density and cardiovascular status need to be considered with chronic use. For example, a weekly intramuscular administration of 400 mg of depomedroxyprogesterone was associated with a reduction in average monthly seizure frequency from 22.5 to 2.4 in a 44-year-old woman with PCO and intractable complex partial seizures of left temporal and right frontal origin. Lower dosages or frequency of administration were less effective.

Oral synthetic progestins administered cyclically or continuously have not proven effective therapy for seizures in clinical investigations,^{74,76} although individual successes with continuous daily oral use of norethistrone and combination pills have been reported.^{77,78}

Clomiphene Therapy

Clomiphene acts as an estrogen antagonist to increase gonadotropin secretion and induce ovulatory cycles in estrogen-secreting anovulatory women who do not have primary pituitary or ovarian failure.⁷⁹ Normalization of reproductive endocrine functions and menstrual cycles among women who have both partial seizures and menstrual disorders with documented inadequate luteal phase has been demonstrated to significantly and sometimes dramatically lessen seizure frequency.^{80,81} In one investigation of 12 women, 10 improved, and seizure frequency declined by 87%.⁸⁰ Clomiphene, however, is a drug with considerable pharmacological potency and potentially disturbing side effects. Therefore, it should be used only after potential risks and benefits are weighed carefully and treatment

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with antiseizure medications and progesterone prove inadequate to control seizures.

HORMONAL THERAPY OF EPILEPSY IN MEN

Toone and associates⁸ found that decreased sexual interest among men with epilepsy was associated with reductions in free testosterone. Fenwick and colleagues²⁸ demonstrated a relationship between decreased potency and low free testosterone levels. Herzog et al.¹⁶ measured abnormally low biologically active, that is non-sex hormone-binding globulin (SHBG)-bound (free plus albumin-bound), testosterone levels in 5 of 8 treated epileptic men with diminished sexual interest or reduced potency. In a subsequent investigation, Herzog and coworkers²⁵ observed that among 13 men with epilepsy, those who were classified as sexually normal had an almost twofold higher average non-SHBG-bound testosterone value than those with reproductive or sexual dysfunction (2.4 vs. 1.4 ng/ml). Nevertheless, only 3 of 8 hyposexual men had levels below the normal control range and the average values of both groups were normal.

Another important endocrine factor may be estradiol elevation. Herzog and coworkers³¹ found total and non-SHBG-bound serum estradiol levels to be significantly higher among phenytoin-treated men with epilepsy than among untreated epileptic men or normal control subjects. A significant linear correlation between serum concentrations of biologically active estradiol and phenytoin, but not albumin or hepatic enzymes, suggests a direct medication effect rather than an indirect cause mediated via drug-induced hepatic dysfunction.⁸² The finding of elevated estradiol raises the possibility that enzyme-inducing antiseizure medications may lower biologically active testosterone not only by the induction of SHBG synthetase, but perhaps also by the induction of aromatase, which converts testosterone to estradiol. Estrogen lowers male sexual interest and function.³¹ Murialdo and associates⁸³ demonstrated significantly higher serum estradiol levels and significantly lower free testosterone to estradiol ratios in hyposexual men with epilepsy than in either normosexual men with epilepsy or normal control subjects. Estradiol exerts a potent inhibitory influence on luteinizing hormone secretion and plays a major role in negative feedback in men as well as women.⁸⁴ Suppression of luteinizing hormone secretion results in hypogonadotropic hypogonad-

ism. Chronically low free testosterone leads to testicular failure and hypergonadotropic hypogonadism. This may explain the frequent occurrence of both of these reproductive endocrine disorders in men with epilepsy.⁷²

Testosterone replacement is the most common form of therapy for hypogonadism. Some reports ascribe anticonvulsant properties to testosterone when used in experimental animals.³³ This view, however, remains controversial. One possible explanation is that while one major testosterone metabolite, dihydrotestosterone, blocks NMDA transmission⁸⁵ and may thereby have antiseizure effects, another metabolite, estradiol, increases seizure discharges.^{33,45,50} Since testosterone increases estradiol, which, in turn, counteracts favorable androgenic influences on reproductive function and epilepsy, inhibition of androgen conversion to estrogen is desirable and can be accomplished by the addition of an aromatase inhibitor.

The combination of testosterone and the aromatase inhibitor, testolactone improves reproductive/sexual function and lessens seizure frequency significantly more than testosterone treatment alone in antiepileptic drug-treated hyposexual men with refractory complex partial seizures and hypogonadism.⁵⁶ This result occurs despite achieving similar serum testosterone levels in both treatment groups. Depotestosterone is administered in doses of 400 mg im biweekly in combination with the oral aromatase inhibitor testolactone 3–500 mg/day (T-TL). Testosterone dosages are adjusted to normalize bioactive testosterone levels. Most men prefer levels in the high normal range for optimal sexual desire and potency. Testolactone dosage is adjusted to normalize abnormally elevated serum estradiol levels to a normal range between 20 and 40 pg/ml. Improvement in sexual function questionnaire scores did not correlate significantly with changes in serum levels of bioactive testosterone but did show a statistically significant inverse correlation with serum estradiol. The greater improvement with combined therapy and the statistically significant inverse correlation between changes in sexual function questionnaire scores and serum estradiol suggest that normalization of estradiol as well as testosterone is associated with greater improvement in sexual function than normalization of testosterone alone. Since estradiol has epileptogenic effects,^{33,45,50} the significantly greater reduction in serum estradiol using combined therapy may also be responsible for the significantly greater reduction in seizure frequency with combined therapy compared with testosterone therapy alone.

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