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Unbalanced progesterone and estradiol secretion in catamenial epilepsy

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Ten women with a documented history of catamenial epilepsy underwent a hormonal study to evaluate hypophyseal-gonadal function. Baseline values of luteinizing hormone, follicle-stimulating hormone and prolactin were similar in catamenial seizure patients and in control groups throughout a complete menstrual cycle. Stimulated secretions of the same hypophyseal hormones in catamenial seizure patients overlapped those of the controls.

The luteal secretion ratio of progesterone to estradiol was significantly reduced in catamenial seizure patients versus normal controls. In a subgroup of catamenial seizure patients on antiepileptic therapy, luteal progesterone levels were remarkably decreased compared to normal and epileptic controls. These results indicate that catamenial epilepsy is characterized by an imbalance in ovarian steroid secretion and emphasize the need for an endocrinological assessment in these patients.

INTRODUCTION

Catamenial epilepsy is an accepted term commonly employed to indicate the clustering of seizures at menses in women with epilepsy throughout fertile age. However, this disorder has not been precisely defined, and its frequency in the population of female epileptic patients varies from 2.3 to 72%, according to different reports[1,2,5,19]. A recent investigation[26] in a group of patients with drug-resistant temporal lobe epilepsy (TLE) failed to confirm an increase of seizures during menses. These discrepancies may depend on the different methodological procedures used or reflect the non-specific nature of the catamenial epilepsy syndrome. The problem is compounded by the difficulty of matching two categories of phenomena, such as menses and seizures, which are variable and at times unpredictable, particularly the latter.

The relationship between seizures and ovarian hormones is mostly based on anecdotal evidence. In 1976 Backstrom[3] demonstrated an inverse relationship between frequency of seizures and plasma progesterone (P) levels in a group of epileptic women. Close scrutiny of his data reveals that a sub-

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group of these patients presented an increase in seizures during menses and a hormonal picture of luteal phase inadequacy. Thus, this correlation is presently based only on a small number of patients. Moreover, the subjects studied were receiving multiple antiepileptic drugs (AEDs) which further undermines the validity of the observation. In fact, AEDs can interact with hypophyseal hormonal secretion and/or with ovarian steroid metabolism (for a review see ref. 23).

To confirm and expand Backstrom's findings, during the last 5 years we have collected clinical and hormonal data from women referred to our institute because of clustering of seizures at menses. The hormonal studies, performed during a complete menstrual cycle in a group of 10 women with a documented history of catamenial epilepsy, confirmed the existence of an impairment of luteal phase, due to decreased P secretion absolute or relative to the estrogen secretion. Some preliminary data have been previously reported[6,7].

MATERIAL AND METHODS

Ten women with a history of catamenial epilepsy and a normal brain CT scan were studied. Catamenial epilepsy was defined as occurrence of seizures in constant temporal relationship with menses, verified for at least 6 months prior to entering into the study: at least 75% of seizures had to occur in an 8–10 day period inclusive of the menses and the 4 days immediately preceding the menses themselves.

Five of these patients had refused or discontinued AED treatment at least 6 months prior to the hormonal investigation (group A1). The remaining 5 patients were receiving AED therapy before and during the study (group A2). Five additional female epileptic patients with no prior history of a relationship between seizures and menses (group B) and 5 age-matched normal women served as controls. Table I reports the details of all patients studied.

TABLE I

Clinical characteristics of women with epilepsy

	Age (years)	*Seizures*			*Therapy*
		*Type**	*Number/cycle*	*Pattern*	
Group A1					
1	17	GM	<3	Catamenial	None
2	21	GM	<3		None
8	22	PC	>10		None
9	23	PC	<3		None
10	38	GM	<3		None
Group A2					
1	16	GM	>3	Catamenial	PB
2	22	PC	>3		CBZ
3	24	PC	>3		PB + CBZ
4	17	Absences	>3		PB + ETX
5	42	PC	>10		PB + CBZ
Group B					
6	17	Absences	>10	Non-catamenial	PB + ETX
7	23	PC	<3		PB
3	24	PC	>3		PB
4	25	GM	<3		PB
5	38	PC	>3		PB + CBZ

* GM, tonic-clonic generalized seizures; PC, partial complex seizures; PB, phenobarbital; CBZ, carbamazepine; ETX, ethosuximide.

Blood samples for baseline hormonal evaluation were collected every 3–4 days at 8 a.m. during an entire menstrual cycle. If a seizure had occurred less than 12 h before sampling time, the blood drawing was delayed to the day after. Serum samples were stored at –20 °C until they were assayed to determine luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), progesterone (P) and estradiol (E2). In each patient stimulatory tests with thyrotropin-releasing hormone (TRH) and gonadotropin-releasing hormone (GnRH) were performed in a randomized succession at the fifth and sixth day of the menstrual cycle. Beginning at 8 a.m., after at least 12 h fasting, 200 μg of TRH (Biodata, Italy) or 10 μg of GnRH (Serono, Italy) were injected (time 0) and blood was sampled at the following times: –15, 0, +15, +30, +45, +60, +90, +120 min. At one time during the cycle, every patient was evaluated for thyroid function by measuring plasma thyroxine and thyrotropic hormone. All hormonal assays were performed by RIA methods as previously described[25]. Calculation of the P to E_2 serum level ratio during luteal phase (PEL), was performed according to a published method[30] as follows: PEL = P(pg/ml)/E_2(pg/ml)×0.01.

A daily seizure record was kept by all subjects. Pharmacological compliance was evaluated throughout the study by means of randomized plasma measurements of AEDs in the patients on therapy.

Statistical analyses of the data were done by ANOVA and Duncan's multiple range test, as appropriate, with $P \leq 0.05$.

RESULTS

The frequency and distribution of seizures throughout the menstrual cycle were similar to those observed during the 6 month period prior to the beginning of the study (Table I) in all patients but one (case no. 2) who did not have seizures. The pharmacologic compliance of the patients was excellent, based on the plasma levels of AEDs

TABLE II

Gonadotropin and prolactin values (mean ± S.E.) during menstrual cycle

LH, luteinizing hormone; FSH, follicle-stimulating hormone; PRL, prolactin.

	*Days from LH peak**							
	–14	*–10*	*–5*	*0*	*+4*	*+8*	*+12*	*+14*
Controls								
LH (mIU/ml)	11.0 ± 2.2	8.8 ± 2.3	11.5 ± 1.5	25.5 ± 5.6	12.2 ± 1.3	11.1 ± 1.2	8.8 ± 1.5	7.5 ± 1.5
FSH (mIU/ml)	5.5 ± 1.2	5.8 ± 1.5	5.5 ± 1.6	16.8 ± 5.5	6.5 ± 2.4	6.7 ± 3.5	4.8 ± 2.9	4.4 ± 1.4
PRL (ng/ml)	8.4 ± 2.4	7.5 ± 1.3	7.8 ± 2.5	8.2 ± 3.3	9.9 ± 3.4	11.0 ± 2.5	10.0 ± 2.5	9.5 ± 2.4
Group A1 (catamenial untreated)								
LH (mIU/ml)	5.5 ± 1.6	8.6 ± 1.5	10.0 ± 1.3	30.0 ± 9.5	16.5 ± 1.3	16.1 ± 3.5	10.0 ± 2.4	10.0 ± 2.4
FSH (mIU/ml)	8.5 ± 2.5	9.4 ± 2.7	11.8 ± 2.4	18.8 ± 6.4	7.8 ± 3.1	6.7 ± 2.4	5.5 ± 3.3	5.5 ± 2.2
PRL (ng/ml)	8.5 ± 1.4	8.8 ± 1.3	7.8 ± 1.2	10.8 ± 3.7	10.0 ± 2.5	7.8 ± 3.5	7.0 ± 1.4	7.7 ± 2.3
Group A2 (catamenial treated)								
LH (mIU/ml)	12.2 ± 3.5	10.9 ± 3.6	11.9 ± 5.7	24.3 ± 9.0	16.0 ± 6.0	12.1 ± 4.0	13.6 ± 6.5	8.9 ± 3.7
FSH (mIU/ml)	7.2 ± 4.4	8.3 ± 4.5	9.2 ± 3.8	12.3 ± 6.5	8.8 ± 1.7	7.3 ± 1.7	8.1 ± 2.5	6.7 ± 3.9
PRL (ng/ml)	11.9 ± 5.2	8.9 ± 1.9	10.6 ± 5.9	15.6 ± 9.0	11.0 ± 3.2	12.0 ± 4.3	12.0 ± 3.7	11.6 ± 6.7
Group B (no catamenial)								
LH (mIU/ml)	11.6 ± 2.5	11.0 ± 2.3	13.0 ± 1.8	29.0 ± 5.5	11.0 ± 1.0	15.5 ± 2.4	11.6 ± 2.3	8.9 ± 1.5
FSH (mIU/ml)	8.8 ± 1.4	7.8 ± 1.3	8.2 ± 2.1	18.1 ± 4.8	9.5 ± 1.5	9.9 ± 1.3	5.5 ± 1.4	4.8 ± 2.4
PRL (ng/ml)	8.0 ± 2.3	8.5 ± 1.5	8.8 ± 1.5	11.0 ± 1.0	13.6 ± 3.2	11.2 ± 3.4	11.9 ± 1.6	9.9 ± 1.5

* Cycles were synchronized around the day of the luteinizing hormone peak = day 0.

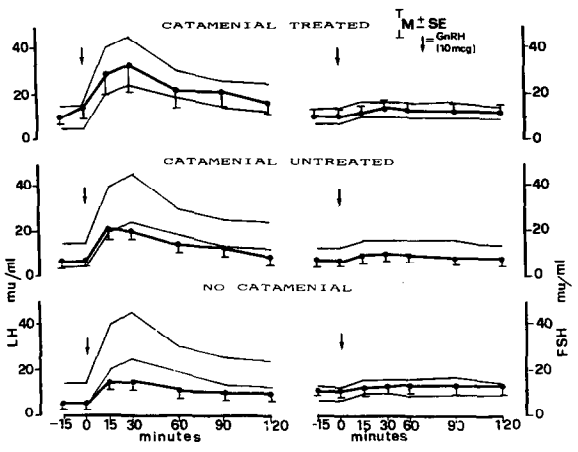

Fig. 1. Luteinizing hormone (LH, left axis) and follicle-stimulating hormone (FSH, right axis) responses to gonadotropin-releasing hormone (GnRH) in epileptic groups. Thin lines indicate hormone values in normal controls (mean ± S.E.). A significant difference in LH response between epileptic (no catamenial seizure patients) and normal controls was present ($P < 0.05$, ANOVA).

which were similar to those obtained prior to the hormonal study. No patients showed any abnormality in thyroid hormonal function (data not shown).

Baseline hormonal levels of all hypophyseal hormones, LH, FSH and PRL, during a complete cycle were similar in epileptic and in control groups (Table II). The LH secretory response to GnRH stimulus was significantly reduced in group B (no catamenial seizures) compared to normal controls, while the FSH secretory response to the same stimulus did not show any difference between epileptic and control groups (Fig. 1). Hypophyseal PRL response to TRH stimulus was present and similar in all epileptic and in control groups (Fig. 2).

E_2 plasma values of the epileptic patients were similar in the different groups and overlapped those of the controls when considering the entire ovarian cycle, as well as follicular or luteal phase separately.

P levels were unmodified during follicular phase in both epileptic and control groups. During luteal phase, P levels proved to be significantly reduced in group A2 (catamenial treated) compared both to group B (no catamenial seizures) and to normal controls (Fig. 3).

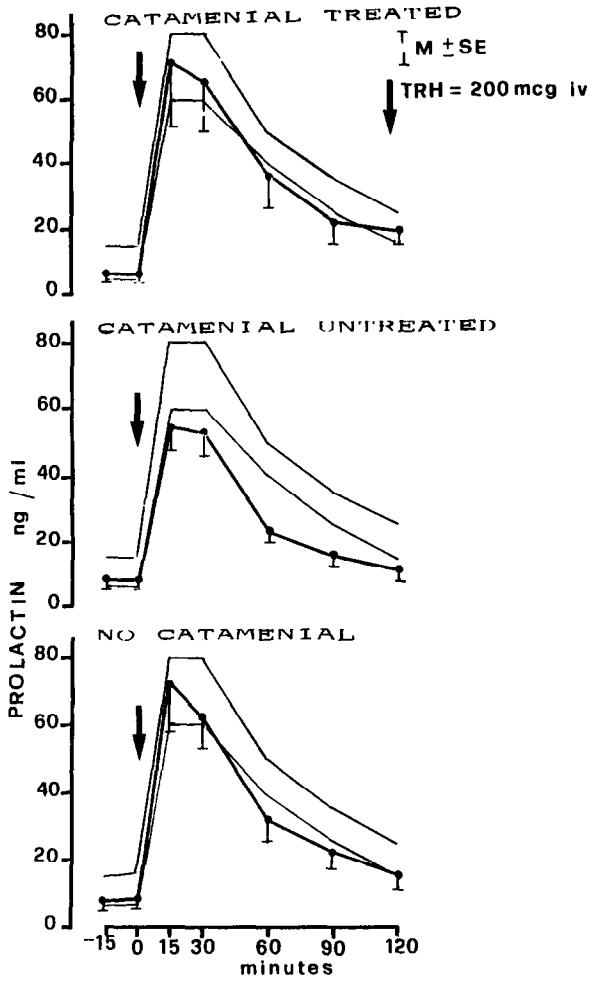

Fig. 2. Prolactin (PRL) responses to thyrotropin-releasing hormone (TRH) in epileptic groups. Thin lines represent hormone values in normal controls (mean ± S.E.). No significant differences were found.

PEL values were significantly reduced in both groups A1 and A2 of catamenial epileptic women (without or with therapy) in comparison to normal controls (Fig. 4).

DISCUSSION

In this study a clear decrease of P secretion during luteal phase in catamenial epileptic women on AED therapy has been found. Moreover, an impairment of P to E_2 luteal secretion ratio (PEL) was present in both catamenial epilepsy groups, with or without AED treatment. Thus, an inadequate luteal phase due to a reduced P secretion, either absolute or relative to E_2, seems to corre-

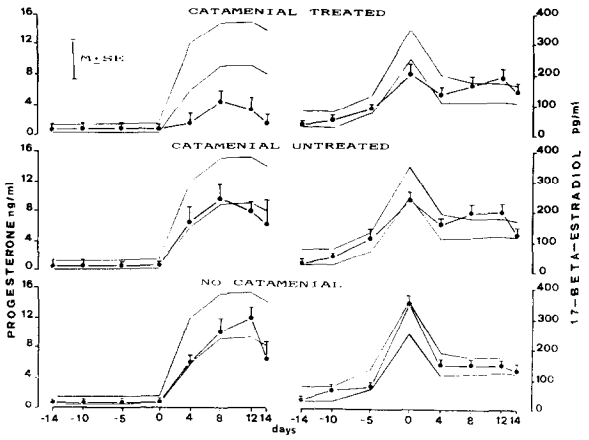

Fig. 3. Baseline progesterone (P, left axis) and 17-β-estradiol (E_2, right axis) values in epileptic groups throughout a complete menstrual cycle. Cycles were synchronized around the day of the luteinizing hormone peak = day 0. Thin lines indicate hormone values in normal controls (mean ± S.E.). P levels were significantly reduced in catamenial seizure patients under treatment compared to no catamenial seizure group and normal controls ($P < 0.01$, ANOVA).

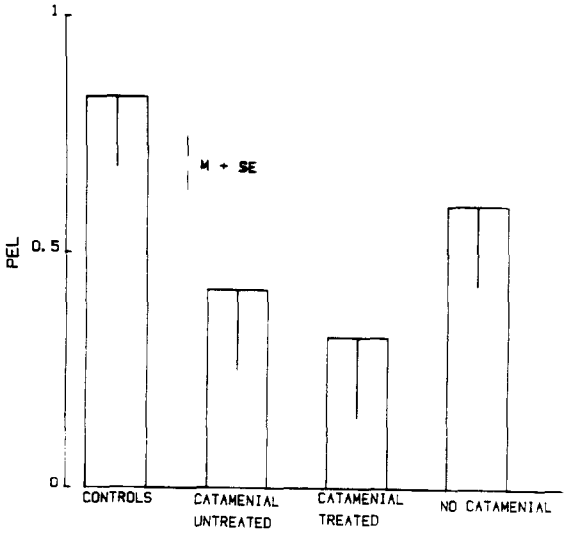

Fig. 4. Progesterone to 17-β-estradiol luteal secretion ratios (PEL; see Methods) in epileptic groups and in normal controls are reported. PEL values were significantly reduced in both treated and untreated catamenial seizure patients compared to normal controls ($P < 0.01$, ANOVA).

late well with the occurrence of catamenial epilepsy.

Recently it has been shown that urinary excretion of estrogen as well as of progesterone metabolites was definitely reduced in patients with seizures either related or unrelated to the menstrual phase compared to normal controls throughout a complete ovarian cycle[29]. However, no clear definition of catamenial epilepsy was given in this study, and the group with menstrual related seizures shows only a 10% increase at the 27th day of the cycle compared to the group without menstrual relationship. Furthermore, all patients in both groups were treated with phenobarbital and phenytoin which are powerful enzymatic inducers. Besides some direct action on the hypothalamic–hypophyseal axis[8,10,13], these drugs are able to modify the hepatic metabolism of sex steroid hormones[9,32,33], eventually decreasing their 24 h urinary excretion. Thus even though a small difference might have existed between the 2 groups, such a difference might have been obscured by the AED treatment.

Our data from patients with catamenial epilepsy without AED treatment demonstrate that the natural history of these disorders is characterized by an imbalance in ovarian steroid secretion. Although not providing a cause–effect relationship, the association of catamenial epilepsy with impaired, absolute or relative P secretion is certainly compatible with such a hypothesis. Seizures per se would be able to modify gonadotropin secretion besides other hypophyseal hormones[12], eventually resulting in changes of ovarian steroids. However, this hypothesis conflicts with the absence in catamenial epilepsy of any seizure-related alterations or hypophyseal hormone secretion during baseline hormonal assessment. A similar impairment of P secretion can be also found in the premenstrual syndrome[28] and in menstrual migraine[15]. Such diversified clinical expressivity of P deficiency could still be compatible with the hypothesis of a multifactorial expression of this hormone imbalance. On the other hand, perimenstrual clustering of seizures is also seen in polycystic ovarian syndrome (PCO), a disorder characterized by an aberrant tonic increase of LH secretion and elevated plasma levels of estrogens[17]. Therefore, since P deficiency is not necessarily associated with catamenial epilepsy and perimenstrual clustering of seizures may be also related to an excess of estrogens, a complete hormonal investigation is warranted in

patients with menstrual related seizures, prior to planning any specific hormonal treatment.

Abundant clinical and experimental data suggest a proconvulsant role for estrogens and the anticonvulsant effects of P, although the intimate mechanism of neuronal excitability regulation by steroid sex hormones has not been elucidated yet. In women with epilepsy, i.v. administered estrogens or P respectively increase[20] or decrease[4] interictal EEG activity within a few seconds, suggesting an effect of sex steroids on neural membranes and/or neurotransmission more direct than the typically slow intracellular activity of these hormones[27].

Recently, it has been reported that physiological P metabolites interfere with GABA receptor in a way similar to barbiturates[22]. P is able to increase GABA inhibitory responses and to suppress the glutamate excitation on Purkinje cells, behaving like benzodiazepines[31]. In addition, P increases GABA binding[21], suggesting that the anticonvulsant effect of this hormone relies on GABAergic activity. According to previous suggestions[14], the most probable hypothesis is that hormones in the brain convey signals by means of a modification in the efficacy of neurotransmitters. Thus, bearing in mind the well proven involvement of GABA in epilepsy[16], a neuromodulatory action of P on GABA synaptic mechanisms can support the apparently crucial role of P in the control of menstrual-related seizures.

The efficacy of synthetic P-like steroids for the treatment of catamenial epilepsy has been tested in preliminary studies. While norethisterone was not able to modify seizure frequency[11], medroxyprogesterone acetate therapy produced a slight but significant reduction of seizures in a group of women with refractory TLE[24]. Interestingly, a remarkable improvement after treatment with natural P in women with TLE, menstrual-related seizures, and endocrine features of PCO or insufficient P secretion has been reported[17]; recently similar results were obtained with clomiphene, an antiestrogenic drug[18]. Thus, favorable therapeutic results with different hormonal agents emphasize the need for an endocrine assessment in these patients, for a rational treatment choice.

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