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Patterns of seizure occurrence in catamenial epilepsy

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The pattern of seizure occurrence was analysed over 44 menstrual cycles in 12 epileptic women who considered they had menstrually related seizures. Two peaks in the daily seizure rate were apparent. A significant increase in seizures occurred during the days of menstrual flow and the two days preceding it, with a second peak in the four days at midcycle. The lowest seizure rate was in the late phase of the menstrual cycle. Daily salivary progesterone levels were assayed in 11 women, and 12 ovulatory and eight anovulatory cycles were identified on this basis. No increase in seizures occurred at midcycle if ovulation did not occur, but the perimenstrual increase took place irrespective of ovulatory status.

Introduction

An association between the stage of the menstrual cycle and epileptic seizure occurrence has been noted in the medical literature for more than a century[9,13]. Several studies of seizure frequency over the menstrual cycle performed in the last three decades have found either an increase in seizure activity in the follicular phase (the early part of the cycle, when oestradiol levels are highest[2,11]) or during the days of menstrual flow and the days immediately preceding them, the 'perimenstrual' phase[12,16]. However, other investigators have found no association, or only an insignificant one, between seizures and the phase of the menstrual cycle in their patients[4,8]. Few studies have analysed consecutive cycles in an individual or have taken into account the possible occurrence of anovulatory cycles[2,16]. However, these studies, performed in single cycles in different women, have indicated that fewer seizures occurred in ovulatory than in anovulatory cycles.

The possible contribution of progesterone and oestradiol in the pathogenesis of epileptic seizure activity has led to trials of these hormonal agents in women with poorly controlled seizure disorders[10,14,22]. These studies have had qualified success in highly selected groups of women. In addition, some reports have found a perimenstrual drop in antiepileptic drug level[18], a finding not confirmed by others[3], but a possible explanation for an increase in seizures at this stage of the cycle.

As part of an ongoing study of the changes in oestradiol, progesterone and antiepileptic drug levels over the menstrual cycle we have analysed the actual patterns of seizure occurrence in women

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with a self-reported increase in seizures in different phases of the menstrual cycle. One aim of this study was to investigate any association between seizure rate and ovulatory status.

Materials and methods

Patients

Twelve epileptic women were studied. Details of their ages, types of epilepsy, medications and number of menstrual cycles studied are given in Table I. None of the women was taking oral contraceptives during the study period. All subjects gave informed consent and the studies were approved by the Ethics Committees of the University of Queensland, the Royal Brisbane Hospital and the Mayo Clinic, Rochester, MN.

Each subject was recruited from the epilepsy clinic because of a strong association noted by the patient between her menstrual cycle and her seizure activity. No distinct pattern of timing relative to the cycle was necessary: for example, the subject may have believed that her seizures were worse at midcycle, or just before menstrual flow.

Each subject maintained a daily seizure diary in which were noted the dates of menstrual flow, details of medication intake and the number of seizures.

In order to determine whether the cycles were ovulatory or anovulatory 11 subjects collected unstimulated saliva into tubes each morning upon awakening. Patients wrote the date of collection on each tube and stored it in a home freezer until collection each month.

Progesterone assay

The concentration of progesterone in saliva was measured using a modification of the Amerlite Progesterone Assay kit (Amerlite, USA) which is a chemiluminescence technique[21]. This kit was designed to measure serum progesterone but was modified to measure salivary progesterone by sub-

TABLE I

The age, type of seizure, medications and number of menstrual cycles studied for each subject

Subject number	Age (years)	Type of seizure	Medication	Number of cycles
1	32	complex partial	CBZ, CBZ, PB	3 3
2	35	secondarily generalized	PHT	5
3	30	complex partial	mePB, PHT	3
4	26	complex partial	PB, PHT	1
5	37	generalized	CBZ	2
6	42	secondarily generalized	PB, PHT	2
7	35	secondarily generalized	PHT	3
8	28	complex partial	PB	1
9	38	complex partial	CBZ	9
10	25	secondarily generalized	PHT	7
11	38	complex partial	CBZ, PHT	3
12	31	secondarily generalized	PB, PHT	2

CBZ, carbamazepine; PB, phenobarbital; PHT, phenytoin; mePB, methylphenobarbital.

stituting saliva spiked with progesterone as calibrators. This yielded a luminescent response similar to that derived from serum-based calibrators. The limit of sensitivity of the procedure was 10 pg/ml (32 pmol/l). The precision at that concentration was 30%. The precision of the assay at 50 pg/ml (160 pmol/l) was 7%. All saliva samples were stored at −20°C until the time of analysis.

Ovulation was considered to have occurred if there was a clear and sustained rise in the progesterone concentration in saliva during the second half of the cycle. The day of ovulation was taken as the day that salivary progesterone concentration first exceeded 50 pg/ml (160 pmol/l).

Data analysis

For most of the data analysis the menstrual cycle was divided into four time periods:

(1) Perimenstrual: the days of menstrual flow and the days before it to give a total of seven consecutive days;

(2) Midcycle: the four days at midcycle where ovulation occurred, as determined by the salivary progesterone level (20 cycles in 11 subjects) or by counting back 14 days from the onset of the next menstrual flow, when the salivary progesterone level was not available (24 cycles). This period included the day before, the day of and the two days after the day of ovulation, as defined above;

(3) Early: the days of the menstrual cycle before the midcycle and corresponding to the follicular phase of an ovulatory cycle;

(4) Late: the days of the menstrual cycle before the perimenstrual period and after the midcycle, corresponding to the luteal phase of an ovulatory cycle.

For each of the phases in all the subjects the seizure rates per day were compared using analysis of variance and any difference was analysed using Dunnett's test. Separate analyses were made of known ovulatory and known anovulatory cycles, as determined by salivary progesterone assays. Any differences between the status of ovulation were analysed using the 'sign' test. Statistical significance was assigned if $P < 0.05$.

Results

A total of 44 cycles in 12 women were analysed. There was a significant difference in the mean number of seizures per day between the four stages of the cycle ($P < 0.0001$, $F(3,136) = 12.59$), with a greater number of seizures in the perimenstrual period compared to the early and late stages ($P < 0.01$) and also a greater number at midcycle compared to the early ($P < 0.01$) and late ($P < 0.05$) stages (Table II). There was no difference in the daily seizure rate between the perimenstrual and midcycle stages.

The daily seizure rate was greater in the perimenstrual period than in the early or late period in 35 of 44 cycles ($P < 0.00001$, sign test), and there was a greater seizure rate in midcycle than in early or late stage in 26 cycles ($P = 0.029$, sign test). Table II shows the mean seizure rate in all subjects, and also in known anovulatory cycles and ovulatory cycles.

In 20 cycles in 11 women the status of ovulation was ascertained using salivary progesterone levels. There were eight anovulatory cycles in six women. In these cycles there was a statistically significant difference in the daily rate of seizures between the four stages of the menstrual cycle ($P = 0.025$, $F(3,26) = 3.90$), with the difference arising from a greater number of seizures in the perimenstrual

TABLE II

The mean (± SEM) seizure rate during the four phases of the menstrual cycle in 44 cycles of 12 epileptic women, and in the eight known anovulatory and 12 known ovulatory cycles

	Early	Midcycle	Late	Perimenstrual
All subjects (n = 44)	0.25 ± 0.07	**0.88 ± 0.21**	0.28 ± 0.08	**0.94 ± 0.16****
Ovulatory cycles (n = 12)	0.14 ± 0.05	**0.73 ± 0.20**	0.11 ± 0.06	**0.97 ± 0.32****
Anovulatory cycles (n = 8)	0.19 ± 0.11	0.19 ± 0.10	0.05 ± 0.03	**0.49 ± 0.18***

The seizure rate in each phase of the cycle was compared using ANOVA, and significant differences are indicated (*$P < 0.05$, **$P < 0.01$), with the significantly different phase (determined by Dunnett's test) indicated in bold type.

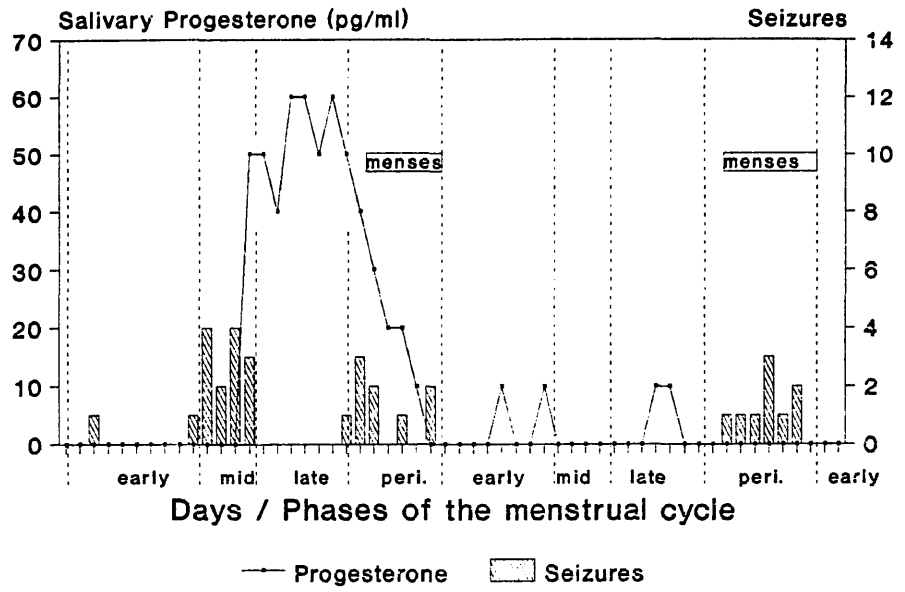

Fig. 1. The number of seizures per day in subject 1 over an ovulatory cycle and an anovulatory cycle. The salivary progesterone level for each day of the cycle is also shown for the ovulatory cycle.

phase compared to the late phase of the cycle ($P < 0.05$). There was no midcycle increase in seizure frequency.

In known ovulatory cycles there were significant differences in the rates of seizure occurrence in the various stages of the cycle ($P = 0.006$, $F(3,44) = 5.01$), with more seizures in the perimenstrual ($P < 0.01$) and midcycle periods ($P < 0.05$) than the early and late stages.

The seizure pattern of individual subjects was in many instances consistent from cycle to cycle, unless the status of ovulation changed (Fig. 1). For example, subject 1 had an increase in seizure activity in the perimenstrual period in all six of her cycles and a midcycle increase in two cycles, both of which were ovulatory. Subject 9 had a perimenstrual increase in all nine cycles, and a midcycle increase in five of the cycles relative to her daily seizure rate in the early and late phases.

There was no statistically significant difference in the overall daily seizure rate when comparing ovulatory and anovulatory cycles in the 20 cycles where the status of ovulation was known (mean daily seizure rate $\pm$ SD: ovulatory cycles = 0.439 $\pm$ 0.333, anovulatory cycles 0.308 $\pm$ 0.202, $t = 1.67$, $P = 0.16$).

Discussion

The patterns of epileptic seizure occurrence across the menstrual cycle have been studied previously, and a perimenstrual increase in seizures has been noted in many reports[1,2,7,12,16]. The current study has confirmed the perimenstrual increase in seizure rate. In addition, a second peak of increased daily seizure rate, but only in ovulatory cycles, occurred at the midcycle. We have traced only one report[11] of increased seizures which occurred 14–16 days after the onset of menses, corresponding to the midcycle increase in seizures we observed, and this report applied to only one subject. Unlike certain workers[2,4] we found no increase in seizures in the follicular or 'preovulatory' phase of the cycle. The measurement of progesterone concentrations in saliva has enabled a determination of whether, and when, ovulation occurred, and provided information to allow an accurate division of the phases of the menstrual cycle in an easy and painless manner.

Saliva has been increasingly used as a biological fluid in which to measure progesterone for both research and clinical purposes. While the absolute levels of salivary progesterone and the saliva: plasma hormone ratio vary slightly, dependent upon assay technique[19] used, measurement of pro-

gesterone in saliva is an accurate and convenient way of determining the occurrence of ovulation[19]. In the one published paper measuring plasma progesterone and oestradiol levels over the menstrual cycle[2], seizure activity was positively correlated with oestradiol levels and the oestradiol:progesterone ratio.

There could be several other reasons for the discrepancies between reports in the literature concerning seizure frequency at different stages of the menstrual cycle. Firstly, some studies involved institutionalised patients who were either untreated or whose type of treatment was not reported[9,12]. It is quite possible that treatment influences the pattern of seizures[16], and for this reason we are currently analysing antiepileptic drug concentrations, hormone concentrations and seizure occurrence in this group of catamenial subjects. Other reports have been based on small numbers of subjects or single cases[11], and in some the statistical methods used were not mentioned[1,15]. One report noted a cyclic pattern of seizures in male epileptic subjects[11]. In addition, there are methodological differences between the different studies. For example, many workers have taken day 1 of the cycle as the day of onset of menstruation and counted backwards, which means that if cycles are of various lengths, pooled data for the early and mid (i.e., ovulatory) phases of different cycles may be out of synchrony, thus obscuring a short period of increased seizure rate. Division of the cycle into four blocks of days, fixing the position of the mid-cycle days (as above), avoids this problem. The 'perimenstrual' phase has been variously defined as the days of menstrual flow plus the two days[12], four days[5] or one day[1] preceding it, and the pre-ovulatory phase has not been defined in some reports[2]. Only two published studies[2,17] and one abstract[7] have measured progesterone levels specifically to identify ovulatory cycles. These reports have indicated a higher seizure frequency in anovulatory cycles, unlike the present study, but also suggest that the occurrence of ovulation influences the seizure pattern. More detailed studies, measuring progesterone, oestradiol and antiepileptic drug concentrations over the menstrual cycle, are needed to fully assess 'menstrually related seizures'.

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