PREMENSTRUAL SEIZURE INCREASE

INFLUENCE OF AGE, DURATION OF DISEASE, SEIZURE FREQUENCY, PREVIOUS COMPLAINT OF PERIMENSTRUAL ACCENTUATION, EEG AND CT SCAN FINDINGS

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SUMMARY — We selected prospectively 80 mentally healthy women at menacme age, with chronic epilepsy and at least one seizure in the month preceding this study. They underwent four EEGs weekly. CT scan of the skull was done in 57 patients (71.25%). Seven patients were excluded because they had no seizures or menses. We registered 5630 seizures during 579 regular menstrual cycles over a 30 month period. Results: — there was a higher incidence of seizures in the premenstrual period ($p<0.001$); — age did not influence the distribution of seizures during the menstrual cycle in the group studied; — patients with 11 or more years of disease showed more accentuation of premenstrual seizures than patients with 10 or less years of disease; — there was no relation between the patients frequency of seizures and the occurrence of premenstrual seizures; — the patients impression of the incidence of seizures not related to menstruation was not confirmed; — patients with abnormal skull CT scans had more accentuation of premenstrual seizures than patients with normal exams; — patients with abnormal EEGs had more premenstrual seizures than patients with normal exams. Our findings suggest that the female sexual hormones alter cerebral excitability when there is an underlying structural pathology shown by CT scan or an electrical cerebral dysfunction revealed by EEG.

Aumento pré-menstrual de crises epilépticas: importância da idade, duração da doença, frequência das crises, queixa prévia de piora perimenstrual das crises, resultado do CT e do EEG.

RESUMO — Selecionamos prospectivamente 80 mulheres epilépticas, sem aparente distúrbio comportamental ou retardo mental, na menacme, com crises epilépticas não completamente controladas. Foram submetidas a 4 EEGs com intervalos semanais. CT-scan de crânio foi realizado em 57 pacientes (71,25%). Sete pacientes foram excluídas por não apresentarem crises ou menstruações, ou por colaboração insatisfatória. Foram registradas 5630 crises epilépticas em 579 ciclos menstruais regulares durante 30 meses. Resultados: — houve maior incidência de crises epilépticas no período peri-menstrual: — a idade não influenciou na distribuição de crises durante o ciclo menstrual no grupo estudado; — pacientes com 11 ou mais anos de doença mostraram maior tendência a crises no período pré-menstrual que pacientes com 10 ou menos anos de doença; — não houve relação entre a freqüência das crises e a ocorrência de crises pré-menstruais; — a negativa da referência prévia de piora perimenstrual pela paciente não mostrou ser dado relevante; — pacientes cujos CT scan foram anormais tiveram tendência a ter crises no período pré-menstrual; — pacientes com EEGs anormais tiveram mais crises no período pré-menstrual quando comparadas às pacientes com EEGs normais. Nossos achados sugerem que os hormônios sexuais femininos modifiquem a excitabilidade cortical, particularmente quando há prévio comprometimento estrutural evidenciado pelo CT-scan ou disfunção elétrica cerebral, pelo EEG.

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The intensification of epileptic seizures during the menstrual period has been well recognized since Gowers 14 (1881), and may affect approximately 50% of women during menacme2i. There is no general agreement on the characterization of catamenial epilepsy. Newmark and Penry23 showed this worsening occuring during, before or after the menstrual period. Criteria characterizing menstrual exarcebation vary and many authors do not objectively define the phases of the menstrual cycle and do not differentiate regular from irregular cycles. Different causes have been proposed: water metabolism L7, hormonal changes 2,3, alterations in the pharmacokinetics of antiepileptic drugs 27,29 „s well as emotional changes 5,19.

We studied the relationship between seizures and menstrual cycles, clinical aspects, EEG and CT scan findings, mainly in women with partial seizures with secondary generalization.

METHODS

Eighty epileptic patients were followed-up from October **1984** through April **1987** and included in the study according to the following criteria: — women m menacme who were able to understand and register seizures and the menstrual cycles in a diary; — patients being followed at the Epilepsy Out-Patient Clinic of the University of Campinas (UNICAMP), São Paulo, Brazil; — patients with work-up consisting of history, physical and neurological examinations, skull X-rays, CSF studies and EEG; — patients without behaviour disturbances or apparent mental retardation; — patients not completely controlled and who had experienced at least one seizure within a period of one month, preceding the initial consultation. Patients socio-eeonomical condition were similar to that of the population attending the UNICAMP Hospital. Seizure classification is showed on Table **1.** Seventy-four patients **(92.5%)** had partial seizures. Fourty-seven **(58.75%),** simple partial seizures; **24 (51.08%)** motor; **20 (42.5%)** autonomic; **11 (23,4%)** psychic; **5 (10.63%)** sensory. Seventy patients **(87.5%)** presented complex partial seizures: **25 (35.7%)** with complex partial onset; **45 (64.3%)** with simple partial onset. Seventy-one patients **(88.75%)** had generalized tonic-clonic seizures, only four of them with primary onset. Four patients **(5%)** had absence seizures: only one of these had exclusively absences. Patients ranged in age between **16** and **47** years (median **28,** mean **28.25).** At the onset of the disease, age varied from a few days to **30** years (mean and median, **10.5** years). Duration of disease ranged from **1** to **42** years (mean **17.5,** median **16).** Possible etiology could be demonstrated in **27** patients **(33.7%): 22** neurocysticercosis **(27.5%); 3** head trauma (with coma lasting over **24** hrs); **1** encephalitis; **1** cerebral palsy. Fourty-six patients received single medication; thirty-one received two medications; three patients received three medications.

5,630 seizures were registered through **745** regular menstrual cycles. We considered a cycle as regular when the interval between the first days of two consecutive cycles varied from **21** to **36** days. Out of **857** cycles, **745 (86.93%)** were regular and **112 (13.6%)** were irregular. We divided the patients in two groups: Group I, **53** patients **(66.25%)** with previous or present complaints of perimenstrwal seizures intensification; Group II, **27** patients **(33.75%)** without. All patients underwent a total of **4** EEGs at the beginning of the study, which were done during four consecutive week interval. The EEGs were classified in normal, abnormality II (slow waves, intermittently) and abnormality III (spikes, sharp waves and spike and wave complexes). A total of **57** CT scans were performed in several radiologic services at different time in the study. In **23** patients the abnormality consisted of single or multiple calcification, mainly due to neurocysticercosis. Seven patients were excluded from analysis:

Partial seizures	**74 (92.5 %)**	**Only SPS**	**2**
		SPS + CPS	**4**
		SPS + CPS + TCS	**41**
		Only CPS	**2**
		CPS + TCS	**23**
		*** PS + TCS**	**2**
Generalized seizures	**6 (7.5 %)**	**Only TCS**	**1**
		Only AS	**1**
		AS + TCS	**4**

Table 1 — Classification of seizures. SPS, simple partial seizure; CPS, complex partial seizure; TCS, tonic-clonic seizure; AS, absence seizure; * PS, indetermined partial seizure.

one got pregnat, three had complete seizure control and three were not cooperative or abandoned the study.

Seizure frequency, as related to period of the menstrual cycle where they occurred, was analysed by contingency tables (chi-square).

RESULTS

There was a higher incidence of seizures in the premenstrual period ($p < 0.001$) (Fig. 1A). Age did not influenced the distribution of seizures during the menstrual cycle ($p < 0.001$). Patients with 11 or more years of disease showed more accentuation of premenstrual seizures than patients with 10 or less years of disease ($p < 0.001$ & $p < 0.44$). (Fig. IB).

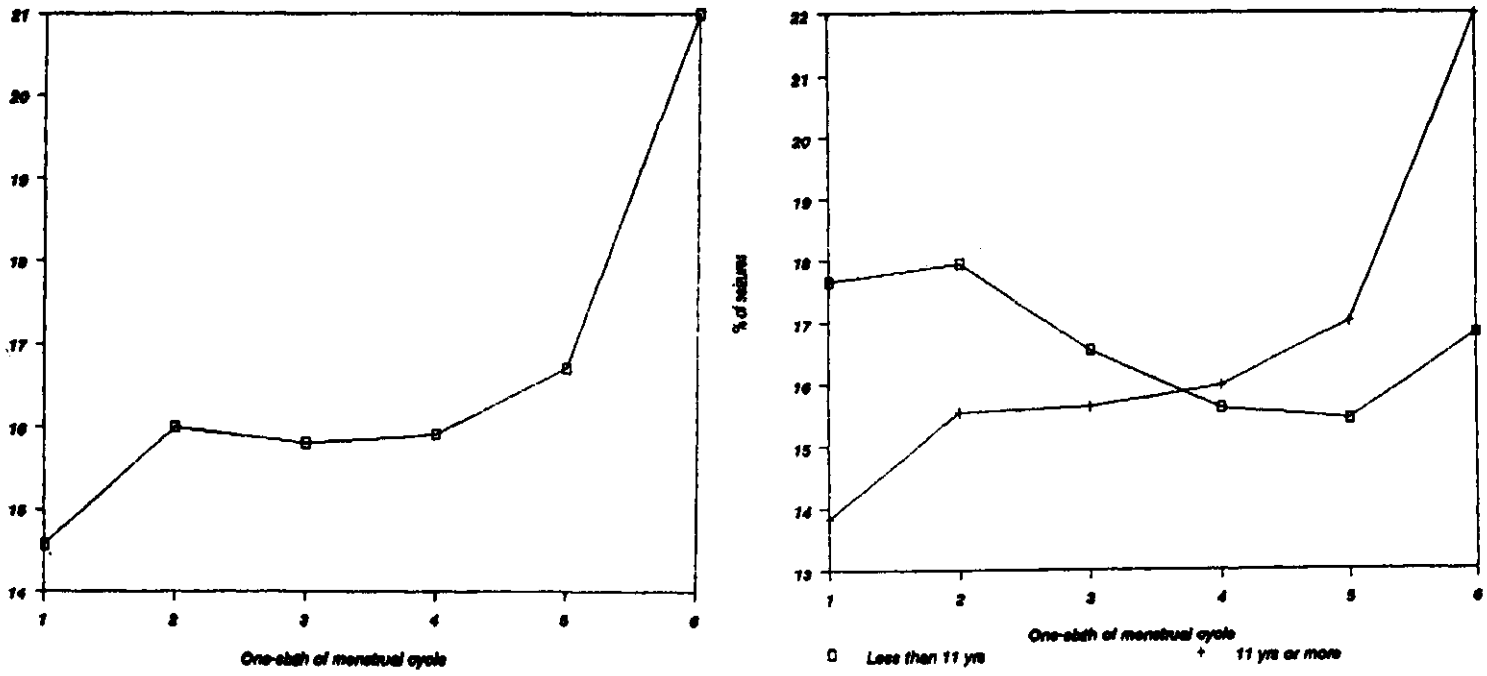

Fig. 1 — A (left). Seizure distribution according to the period of menstrual cycle (a period equals one sixth of the total duration ($p<0.001$). B (right). Seizure distribution according to its occurence in the menstrual cycle and duration of disease ($p<0.001$).

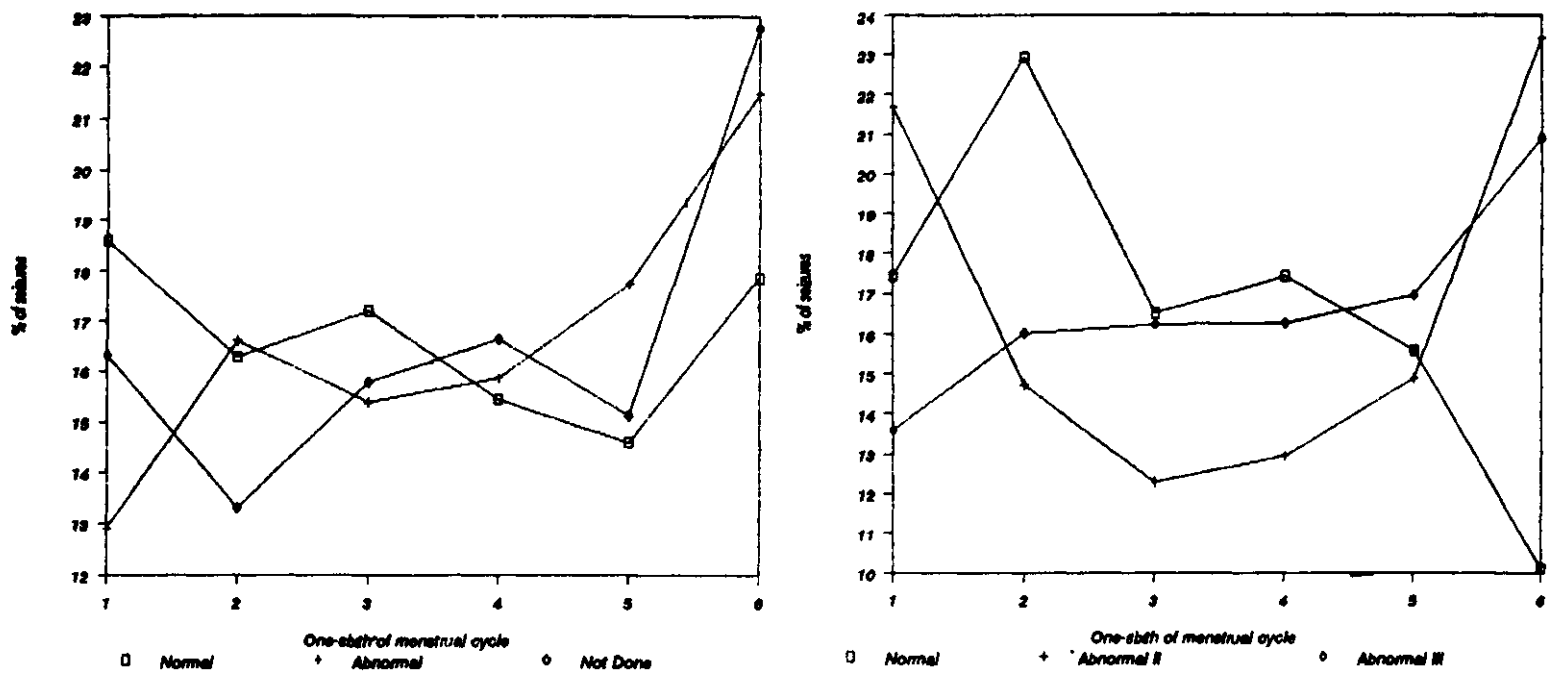

Fig. 2 — A (left). Seizure distribution according to its occurrence in the menstrual cycle and CT-scan findings ($p<0.001$). B (right). Seizure distribution according to its occurrence in the menstrual cycle and EEG findings ($p<0.001$).

The frequency of seizures out of the premenstrual period did not influence the occurrance of premenstrual seizures ($p < 0.001$). The patients impression of the incidence of seizures not related to menstruation was not confirmed ($p < 0.001$ & $p=0.004$).

Patients with abnormal skull CT scans had more accentuation of premenstrual seizures than patients with normal exams ($p<0.001$ & $p=0.14$) (Fig. 2A).

Patients with abnormal EEG had more premenstrual seizures than patients with normal exams ($p<0.001$ & $p = 0.03$). (Fig. 2B)

COMMENTS

Even though we based our study on clinical diagnosis of epilepsy, we think our conclusions are valid for several reasons: the long disease duration, i.e., a minimum of 1 year, with mean of 17.5 years; the frequency of seizures and most patients with abnormal EEGs. Of the 80 patients, 75 (93.75%) had focal epilepsy and 5 (6.25%) had idiopathic generalized epilepsy. The latter were easily controlled. Therefore, the main focus of this study was on patients with focal seizures, with or without secondary generalization. The relatively high age mean (28.25 years) and the duration of disease (mean 17.5 years) indicate that this is a characteristic subgroup among the epilepsies.

We can expect mistakes in a clinical study depending on patients registering in a diary the occurrence of seizures and relating them to the respective portion of the menstrual cycle. We suppose that the recognition of tonic-clonic generalized seizures is easy for the patients, however the same is not true for partial attacks, especially when numerous, increasing, therefore, the chance of error. It is unlikely that a patient registers more seizures than he really had. Neugebauer et al.[24] demonstrated that seizure diaries are reliable, by backing them up wiht other methods. The use of diaries in a low socio-educational population like ours might be questionable. Nonetheless, the possibility of errors is probably diminished by the large number of seizures and menstrual cycles studied. Another problem is the patients cooperation as time goes by. Some patients become less motivated as they experience improved seizure control. The same lack of motivation occurs when this control is less satisfactory. Besides, some patients could add together pseudo and true seizures. Patient 80, who presented a hysterical attack during a consultation, is a good example of the latter. She recognized it as a non-epileptic episode and said that she would have registered the same as a «different attack». Other patients, however, might not have the same good judgement.

The characterization of the phases of the menstrual cycle follows physiological and dynamic concepts, even though they are arbitrary H.25,26,30. **it is difficult to compare different studies from the literature, due to the lack of a definition of the phases of the cycle, of the seizure types and of what they consider exacerbation. Therefore, it also becomes difficult to compare different subpopulations of epileptics from the etiological, age, socio-economical and racial standpoints.**

Approximately half of the patients had normal CT scans. This is in agreement with the literature: CT scan abnormalities varied from 35.3 to 63% 6,8,12,13,20,22 **The highest incidence is found in partial epilepsies. Our patients showed high incidence of neurocysticercosis (26.25%). It should be emphasized that this is the probable etiology in 15% of the seizure patients in our Epilepsy Out-Patient Clinic** 26.

In spite of the limitations pointed out, we are convinced that there is significant increase in the number of seizures in the premenstrual period (late luteal phase). We should point out that we studied only regular cycles, since, in irregular cycles it is difficult to establish a relationship between seizures and phases of the menstrual period.

Age did not influence severity of seizures.

In regards to duration, patients with 11 or more years of disease had a more severe premenstrual seizure intensification than patients with less than 10 years of evolution. Many patients with poorly controlled partial epilepsy had previous history of status epilepticus and periods of time with frequent seizures. Such patients show more severe neuropsychological, intellectual, emotional and social problems 9. It is con-

ceivable that frequent and severe seizures could cause additional brain damage. Recently, Dreifuss[10] analysed epilepsy as a progressive condition and considered several factors as responsible for the neurological deterioration: the underlying lesion as part of a progressive process; neuropathological effect of the seizures (mesial temporal sclerosis); secondary epileptogenesis inducing mirror foci and kindling; chronic drug treatment causing progressive symptoms.

We could not find information in the literature relating frequency of seizures with severity of catamenial epilepsy. In our study, seizure frequency did not have a relationship with premenstrual worsening.

The relationship of seizures with the phase of the menstrual cycle is important, since, irrespective of the complaint, the premenstrual accentuation occurred in both patient groups. So according to Guerreiro et al.[15] we cannot trust in questionnaires to validate this relationship. Besides, the association seizure-menstruation could be fortuitous [4].

The presence of abnormal CT scans in patients with higher incidence of premenstrual seizures reinforce the impression that organicity is an important factor in this phenomenon.

Estrogen and progesterone have been proved to play a role in caiamenial seizures [15]. A direct epileptogenic effect of estrogens has been suggested, especially in the presence of a preexisting cortical lesion [17]. However, Marcus et al.[14] observed that I.V. injection of estrogen in cats had minimal effect upon epileptiform activity, except when there was damage to the blood-brain barrier and previously established cortical epileptogenic focus. The observation that patients with abnormal EEG showed more tendency to prementrual worsening reinforce the latter impression.

In summary, our study could reinforce the impression that female sexual hormones modify cerebral cortical excitability, particularly in the presence of previous structural lesion (CT-scan) or electrical dysfunction (EEG).

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