Arq Neuropsiquiatr 2005;63(3-B):751-756

MENSTRUAL CYCLE WORSENING OF EPILEPTIC SEIZURES IN WOMEN WITH SYMPTOMATIC FOCAL EPILEPSY

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ABSTRACT- *Introduction:* Hormonal fluctuation is responsible for worsening of epileptic seizures during the menstrual cycle. *Objective:* To identify irregularities in the menstrual cycles of women with mesial temporal lobe epilepsy (MTLE) and extratemporal focal epilepsy (ETFE) and correlate the frequency of seizures during the menstrual cycles. *Method:* We evaluated prospectively women in the menacme with MTLE and ETFE. Calendars were provided for these patients, and they were asked to mark their seizure frequency according to the menses. Calendars were reviewed in each routine medical appointment. *Results:* Thirty-nine patients with MTLE and 14 with ETFE were evaluated. We registered 211 cycles in the patients with MTLE and 49 in those with ETFE. Irregular menstrual cycles were found in 28 (28/39, 71.7%) patients with MTLE and 6 (6/14, 42.8%) with ETFE (p=0.052). Premenstrual seizure worsening was observed in 46 (21.8%) patients with MTLE and 9 (18.3%) with ETFE (p=0.596). Menstrual worsening was observed in 47 (22.2%) patients with MTLE and 15 (30.6%) with ETFE (p=0. 217). Ovulatory worsening was observed in 36 (17%) patients with MTLE and 13 (26.5%) with ETFE (p=0,126). Catamenial worsening was observed in 58 (27.4%) of the patients with MTLE and in 17 (34.7%) of the patients with ETFE (p=0.315). *Conclusion:* There was no difference between the group of patients with MTLE and ETFE regarding the frequency of irregular cycles and seizure worsening during the premenstrual, menstrual, catamenial or ovulatory periods.

KEY WORDS: epilepsy, catamenial, temporal lobe epilepsy, extra-temporal epilepsy, menstrual cycle.

Piora de crises epilépticas durante o período menstrual em mulheres com epilepsia focal sintomática

RESUMO - *Introdução:* Admite-se que a flutuação hormonal seja a responsável para a piora de crises epilépticas no período catamenial. *Objetivo:* Identificar irregularidades nos ciclos menstruais de mulheres com epilepsia de lobo temporal mesial (ELTM) e epilepsia focal extratemporal (EFET); e relacionar a frequencia de crises durante o ciclo menstrual. *Método:* Avaliamos mulheres na menacme, que apresentem quadro clínico laboratorial compatível com ELTM e EFET. Foram fornecidos calendários para estas pacientes e instruídas para preenchimento correto da menstruação e das crises epilépticas e serão revistos em cada consulta médica rotineira. *Resultados:* Foram avaliadas 39 pacientes com ELTM e 14 com EFET. Registramos 211 ciclos nas pacientes com ELTM e 49 nas com EFET. Ciclos menstruais irregulares foram apresentados por 28 (71,7%) pacientes com ELTM e 14 (42,8%) com EFEP (p=0,052). Piora pré-menstrual foi observada em 46 (21,8%) pacientes com ELTM e 9 (18,3%) com EFET (p=0,596). Piora menstrual foi observada em 47 (22,2%) pacientes com ELTM e 15 (30,6%) com EFET (p=0,217). Piora ovulatória foi observada em 36 (17%) pacientes com ELTM e 13 (26,5%) com EFET (p=0,126). Piora catamenial foi observada em 58 (27,4%) das pacientes com ELTM e em 17 (34,7%) das pacientes com EFET (p=0,315). *Conclusão:* Não houve diferença entre os grupos de pacientes com ELTM e EFET quanto à freqüência de ciclos irregulares e piora das crises nos períodos pré-menstrual, menstrual, catamenial ou ovulatório.

PALAVRAS-CHAVE: epilepsia, catamenial, epilepsia de lobo temporal, epilepsia extratemporal, ciclo menstrual.

Epilepsy has an estimated prevalence between 1 and 1.8%[1-3]. The incidence of epilepsy in women is similar to that in men. Anovulatory cycles are more frequent in women with epilepsy. In addition, it seems that epileptic seizures are more frequent in anovulatory cycles than in normal cycles[4]. There are reports that up to 50% of women with epilepsy in the menacme present worsening of seizures through the menstrual cycle[5].

Herzog et al.[6] described three standards of sei-

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Received 16 November 2004, received in final form 21 March 2005. Accepted 9 May 2005.

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zure worsening related to different periods of the menstrual cycle: a) seizures that occur during the three days before menses and on the first three days of menses; b) seizures that occur close to the middle of the cycle, before the ovulation between the 8th and 14th days; c) seizures that are frequent between the 8th day of a cycle and the 2nd day of the next; these cycles are anovulatory. This last standard is more difficult to identify, comparing to those that occur in normal menstrual cycles. Experimental studies showed that estrogen is epileptogenic and progesterone protects against seizures[7]. Epileptiform activity is observed during menses, on the days that precede it and in the middle of the menstrual cycle. Patients with both partial and generalized epilepsies present catamenial seizure worsening[8].

The objective of this study was to identify irregularities in the menstrual cycles of women with mesial temporal lobe epilepsy (MTLE) and extratemporal focal epilepsy (ETFE), and correlate the frequency of seizures during menstrual cycle.

METHOD

Women in fertile age were evaluated. Patients were seen at the epilepsy clinic of our University Hospital.

MTLE was characterized according to clinical end electroencephalographic criteria established by the ILAE[9]. Patients presented seizures with epigastric sensation, nausea, autonomic signs, eructation, pallor, facial flush, activity break, pupillary dilatation, fear, panic and olfactory and gustative hallucination[9]. Neuroimaging evaluation by high resolution showed hippocampal atrophy and hyperintense T2 signal indicating mesial temporal sclerosis.

ETFE was based on clinical, EEG and neuroimaging findings of frontal, parietal and occipital epilepsy[10,11].

Every patient was submitted to a questionnaire concerning gynecological and obstetrical antecedents and detailed menstrual history. In addition they were asked to fill out of the calendar regarding the menstrual period.

We considered as irregular cycles the ones shorter than 26 days and longer than 32 days of duration.

Inclusion criteria – a) Women in the menacme with MTLE and ETFE diagnosis according to the criteria of the ILAE for at least one year[9] ;b) MRI and EEG investigation performed at our institution; c) Good compliance to the treatment and available telephone for contact if needed; d) Attendance to clinical follow-ups regularly; e) Fill out the calendar properly; f) Absence of hormonal therapy or the use of valproate; g) Signature of informed consent submitted and approved by the Research Ethics Committee of the institution.

Analysis of the data – The analysis of the data was based on the different periods of the menstrual cycle. The average of crises per day was calculated for each period and compared to other days of the cycle. We estimated worsening when the average of seizure/day in a determined period of the cycle was higher than the either average of the other days or twice or three times the average.

Table 1. Patients with extratemporal focal epilepsy.

N*	Age (years)	Menarc (years)	First seizure	Type	Epileptiform EEG	Normal EEG	MRI	Drugs in use
1	40	12	19 years	SPS/CPS/GTCS	YES	NO	normal	LTG 400mg/CBZ 1000mg
2	35	15	11 years	SPS/CPS/GTCS	YES	YES	L sulcus atrophy	CBZ 1600mg/CLB 10 mg
3	25	13	4 years	CPS	YES	NO	double cortex	CBZ 1200mg/VGB 750mg/ TIORAZIDE 50mg
4	20	13	4 years	GTCS	YES	NO	bilateral occip gliosis	CBZ/TPM/CLN
5	26	14	1y 8month	SPS/CPS/GTCS	NA	NA	PNH RTO cortical	CLB 10/TOPAMAX 100
6	32	NA	8 years	SPS/CPS/GTCS	YES	NO	displasy	PB 300mg/CLB 40mg
7	40	12	9 years	SPS	YES	NO	normal	CBZ 600mg
8	22	14	6 years	SPS/CPS	YES	NO	R frontal gliosis	CBZ 600mg/ CLBl 40mg
9	28	14	14 years	SPS/CPS/GTCS	YES	YES	LOR dural AVMF	CBZ 400mg
10	34	11	4 years	SPS/CPS.	YES	NO	neurocisticercosis	OXC 2100/CLB 40
11	36	10	9 years	SPS/CPS/GTCS	YES	NO	calosotomy	CBZ 1200mg/VPA 1500mg/CLB 20
12	30	9	27 years	SPS/CPS/GTCS	NO	YES	NA	OXC 600mg/PHT 100mg
13	41	12	13 years	SPS/CPS/GTCS	YES	NO	CDMF in LFR	OXC 1800 mg
14	25	13	7 years	CPS	YES	NO	normal	CBZ 1200mg/CLB 60 mg/AMT 75mg

SPS, simple partial seizure; CPS, complex partial seizure; GTCS, generalized tonic-clonic seizures; HÁ, hipocampal atrophy; R, right; L, left; NA, not available; AVMF, arterial-venous malformation; R- region; O- occipital; T- temporal; F-frontal; CDMF, cortical development malformation; Cort, cortical; PNH, periventricular nodular heterotopy; CBZ, carbamazepine; CLB, clobazam; OXC, oxcarbazepine; LGT, lamotrigine; PHT,phenytoin; VPA, valproate; PB, phenobarbital; ETX, etossuximide; TPM, topiramate; CLN, clonazepam; AMT,amitriptiline, MRI, magnetic resonance imaging.

Table 2. Patients with temporal lobe epilepsy.

N*	Age (years)	Menarc (years)	First seizure	TypeYPE	Epileptiform EEG	Normal EEG	MRI	Drugs in use
1	47	15	15 years	SPS/CPS/GTCS	NO	YES	RHA	CBZ 1200mg/CLB 20mg
2	42	15	3 years	CPS	YES	YES	LHA	CBZ 1200mg/CLB 40mg
3	25	12	14 years	SPS/CPS/GTCS	YES	NO	RHA	CBZ 600 mg/LGT 200mg/CLB 30mg
4	37	13	13 years	SPS/CPS	NA	NA	NA	PHT 200mg/ CLB 10 mg
5	36	13	4 years	SPS	YES	NO	LHA	CBZ 1400mg/CLB 20mg
6	39	13	20 years	SPS/CPS/GTCS	YES	NO	LHA	CBZ 600mg
7	33	15	18 years	SPS/CPS	YES	NO	LHA	CBZ 800mg/CLB 20mg
8	39	14	8 years	CPS/GTCS	YES	NO	LHA	CBZ 800mg/CLB 20mg
9	36	13	2 years	CPS/GTCS	YES	NO	LHA	CBZ 1200mg/VPA 600mg/LGT 250mg/CLB 20mg
10	22	11	14 years	CPS/GTCS	YES	NO	LHA	CBZ 600mg
11	24	12	NA	SPS/CPS/GTCS	YES	YES	RHA	PB 150mg
12	38	18	20 years	SPS/CPS/GTCS	NO	YES	normal	CBZ 1000mg
13	20	13	15 years	SPS/CPS	NO	YES	LHA	CLB 20mg/CBZ1000mg
14	20	12	10 years	SPS/CPS/GTCS	YES	YES	LHA	CBZ 1200mg
15	43	10	1 year	SPS/CPS	YES	YES	RHA	OXC 2100 mg/CLB 30mg
16	42	12	2 years	CPS/GTCS	YES	YES	RHA	CLB 30mg/OXC 600mg
17	37	13	3 years	SPS/CPS	YES	YES	RHA	CBZ 800mg/CLB 10mg
18	38	13	24 years	SPS/CPS/GTCS	YES	YES	RHA	PB 250 mg/CLB 20mg
19	48	12	26 years	SPS/CPS/GTCS	YES	NO	NA	CBZ 600mg
20	42	14	7 years	SPS/CPS/GTCS	YES	YES	LHA	CBZ 600mg
21	30	10	11 years	SPS/CPS/GTCS	NO	YES	LHA	CBZ 1300mg/CLB 40mg
22	42	14	18 years	SPS	YES	NO	NA	ETX 750mg
23	30	12	4 years	CPS/CPS/GTCS	YES	NO	NA	CBZ 1100mg/CLB 20mg
24	33	13	1 year	SPS/CPS/GTCS	YES	YES	RHA	CBZ 1200mg/CLB 30mg
25	46	13	15 years	CPS	YES	YES	LHA	CBZ 1000mg/CLB 20mg
26	17	10	7 years	CPS/GTCS	YES	NO	LHA	CLB 20mg/ CBZ 1200mg
27	39	12	11 years	CPS	YES	NO	RHA	CBZ1200mg
28	40	10	2 years	SPS/CPS/GTCS	YES	NO	RHA	CBZ 1200mg/CLB 10mg
29	33	11	25 years	SPS/CPS/GTCS	YES	YES	RHA	CBZ 800mg
30	28	14	1 year	CPS	YES	NO	LHA	CBZ 1000mg
31	36	13	13 years	SPS/CPS	YES	YES	RHA	CBZ 1000mg/CLB 10 mg
32	38	11	14 years	CPS	YES	NO	cerebellar atrophy	CLB 40mg/CBZ 900mg/ NORTRIPTILINE 60mg
33	28	12	7 years	SPS/CPS/GTCS	YES	NO	RHA	CBZ 1200mg/ CLB 40mg
34	34	14	28 years	SPS/CPS/GTCS	YES	NO	normal	OXC 600mg/CLB 20mg
35	30	12	4 years	SPS/GTCS	YES	YES	LHA, neurocisticercosis	CBZ 800mg/CLB 10 mg
36	40	14	3 years	SPS/CPS/GTCS	YES	NO	RHA	CBZ 1200mg
37	42	15	11 mounths	CPS/GTCS	YES	NO	RHA	CBZ 1200mg
38	22	11	16 years	SPS/CPS/GTCS	NO	YES	Normal	CBZ 400mg/CLB 10mg
39	35	12	4 years	SPS/CPS/GTCS	YES	NO	BilateralHA	CBZ 400mg/VPA 2000mg

SPS, simple partial seizure; CPS, complex partial seizure; GTCS, generalized tonic-clonic seizures; HA, hipocampal atrophy; R, right; L, left; NA, not available; AVMF, arterial-venous malformation; CBZ, carbamazepine; CLB, clobazam; OXC, oxcarbazepine; LGT, lamotrigine; PHT,phenytoin; VPA, valproate; PB, phenobarbital; TPM, topiramate; CLN, clonazepam; MRI, magnetic resonance imaging.

Premenstrual period: three days before the first day of the cycle (the menstruation first day).

Menstrual period: period when there was bleeding until the fifth day.

Ovulatory period: period of 5 days, 14 days before the menstruation ± 2 days.

Catamenial period: premenstrualperiod + menstrual period.

Catamenial worsening: three-fold increase in seizure frequency in relation to the other days of the cycle.

Statistical analysis was performed using the Chi-Square test.

RESULTS

Thirty-nine patients with MTLE and 14 with ETEF were evaluated (Tables 1 and 2). We registered 211 cycles in patients with MTLE and 49 in those with ETFE.

Irregular menstrual cycles were presented by 28 (28/39, 71.7%) patients with MTLE and 6 (6/14,

Table 3. Presence of regular and irregular menstrual cycles, and registered seizures in patients with ETFE.

Identification	# of registered cycles	# of registered seizures	regular cycle 26-32 days	irregular cycle <26 ou >32days
1	2	21	1	1
2	1	0	0	1
3	8	114	4	4
4	4	71	3	1
5	5	2	5	0
6	1	7	1	0
7	2	17	2	0
8	2	282	2	0
9	5	0	5	0
10	2	404	2	0
11	4	83	3	1
12	2	7	2	0
13	5	0	5	0
14	6	26	3	3

42.8%) with ETFE (p= 0.052). Information related to seizure counting and regular and irregular menstrual cycles are in Table 3 and 4. Menstrual worsening was observed in 46 cycles (21.8%) of patients with MTLE and 9 cycles (18.3%) of patients with ETFE (p= 0.596). Menstrual worsening was observed in 47 cycles (22.2%) of patients with MTLE and 15 cycles (30.6%) of patients with ETFE (p= 0.217). Ovulatory worsening was observed in 36 cycles (17%) of patients with MTLE and 13 cycles (26.5%) of patients with ETFE (p= 0.126).

Catamenial increasing of seizures (seizures predominantly on the pre and menstrual cycles) was observed in 58 cycles (27.4%) of patients with MTLE and in 17 cycles (34.7%) of patients with ETFE (p=0.315). Catamenial worsening (according to our definition of three-fold increase in seizure frequency in relation to the other days of the cycle) was present in 29 (13.7%) of the patients with MTLE and 4 (8.1%) of the patients with ETFE (p= 0.290)

DISCUSSION

Catamenial epilepsy refers to seizures related to menstrual cycle and affects approximately m 10-70% of women with epilepsy, depending on the definition of worsening[6]. Experimental studies demonstrated that the ovarian steroid hormones affect the neuronal excitability, that way they give support to a biologic base for these fluctuations in epilepsy that occur in association with the menstruation, from the menarche to the menopause[12-19]. The low levels of progesterone in the menses, the rising of estrogen level in the ovulation and low levels of progesterone during the luteal phase of anovulatory cycles are among the several factors that precipitate the catamenial epilepsy. These factors result in the elevation of the estrogen/progesterone ratio[20]. A decrease on serum levels of the antiepileptic drugs on the days that precede the menstruation, can also contribute for the premenstrual exacerbation of the seizures. It is supposed that the lower serum levels of antiepileptic drugs is due to an increase in their metabolism by the hepatic microsomal enzyme system that involves the gonadal steroid metabolism[19].

Mattson et al.[4] reported an increase in seizure frequency during the anovulatory cycle, mainly during the estrogen peak. Jansen and Vaernet[21] related larger incidence of amenorrhea in women with MTLE than in the general population of women. Our data showed that one third of patients evaluated presented catamenial seizure worsening; if we accept the definition proposed by Herzog et al.[6] - higher frequency of seizure on the catamenial (pre + menstrual) period than that of the rest of the cycle.

We evaluated the menstrual disorders in patients with MTLE and ETFE because of the fact that these conditions are well-defined electro-clinic syndromes[10,11,22,23]. These two forms of lesional epilepsies, frequently refractory to the antiepileptic drug (AED) treatment, were evaluated in women who did not use hormone therapy or sodium valproate. It is confirmed that the use of valproate increases the occurrence of anovulatory cycles, mainly in wo-

Table 4 - Presence of regular and irregular menstrual cycles, and registeredseizures in patients with MTLE.

Identification	#of registered cycles	#of registered seizures	regular cycle 26-32 days	irregular cycles <26 ou >32days
1	5	5	2	3
2	6	13	1	5
3	4	86	2	2
4	7	25	3	4
5	3	0	3	0
6	4	10	4	0
7	19	132	13	6
8	6	41	6	0
9	6	20	3	3
10	2	0	2	0
11	17	52	1	16
12	2	0	1	1
13	13	3	3	3
14	4	94	3	1
15	11	11	6	5
16	6	20	3	3
17	6	30	5	1
18	1	0	0	1
19	3	9	3	0
20	5	6	2	3
21	5	0	5	0
22	2	166	1	1
23	2	10	2	0
24	2	10	1	1
25	7	13	3	4
26	3	50	3	0
27	2	12	0	2
28	3	0	2	1
29	10	1	8	2
30	5	4	5	0
31	5	13	5	0
32	3	30	2	1
33	3	0	2	1
34	12	46	11	1
35	5	7	2	3
36	9	212	5	4
37	5	36	3	2
38	2	2	2	0
39	3	11	1	2

men with generalized idiopathic epilepsy[24,25]. Theoretically, the group of patients with limbic lesions (MTLE) would be more inclined to hormonal dysfunctions originated from the influence of limbic structures on the hypothalamus and hypophysis and the consequent hormonal disorder and possible influence on the menstrual cycle.

Anovulatory cycles occur in 14 to 39% on the diverse forms of epilepsy in women[26,27]. According to the methodology utilized, we did not evaluate the patients under the endocrinologic point of view (if the irregular cycles observed were anovulatory or not). Nevertheless, it is known that 11% of women with epilepsy have cycles with intervals out of the period of 21-35 days, which is larger than what is expected on the general population, about 2%[26,28,29]. We adopted the period of 26-32 days for the definition of regular cycles based on the Herzog and Friedman's findings[26], who found significant increase of anovulatory cycles out of this period. It

is known that the irregular cycles have higher probability of being anovulatory[26]. The irregular cycle finding has clinic importance because the frequency of epileptic seizures is higher in these cycles[6,20]. In addition, the incidence of reproductive endocrine disorders is higher in these women[30-32], particularly the polycystic ovary syndrome[32-34]. These disturbances are associated with an increase of the infertility rate, migraine, emotional disturbances, resistance to insulin, cardiovascular disease and cancer[35]. The real role of the irregular or anovulatory cycles in these patients and their medical dimension need complementary investigations.

A recent study about long-term reproductive endocrine health in young women with epilepsy during puberty have shown that 56% patients taking antiepileptic medication, 32% of patients without drugs and 38% normal control presented irregular menstrual cycles. They defined irregular cycle if the intermenstrual variation was > 7 days or the cycle duration was >35 days or <21 days, at least once during the preceding 6 months. In the same study, Mikkonen et al.[36] found that polycystic ovary syndrome was more common in patients on medication (38%, mainly valproate) than in patients without medication (6%) or in controls (11%). These authors[36] proposed that irregular menses may be considered an adverse event of antiepileptic drug treatment, particularly in puberty.

There was no seizure worsening difference on the premenstrual, menstrual, catamenial or ovulatory periods in the two groups of patients we studied. This is a preliminary study and a larger sample should be evaluated in order to confirm our findings.

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