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CASE REPORT

Cyclical excitability of the motor cortex in patients with catamenial epilepsy: A transcranial magnetic stimulation study

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Summary

Purpose: The pathophysiology of catamenial epilepsy is still unclear. Therefore, we investigated the cortical excitability of women with catamenial epilepsy during different phases of the menstrual cycle.
Methods: Using transcranial magnetic stimulation, six patients suffering from catamenial epilepsy were investigated during ovulatory cycles. On days 8, −14, −7 and 2 of the cycle (day 1 being the first day of menstrual bleeding), resting motor threshold (RMT), cortical silent period (CSP), intracortical inhibition (ICI) and intracortical facilitation (ICF) were investigated. The non-parametric Friedman-test for multiple comparisons and Wilcoxon signed rank test were used for statistical analysis.
Results: Five patients suffered from focal epilepsy (three right hemispheric, one bitemporal, one unknown origin) and one patient had idiopathic generalized epilepsy. All patients experienced perimenstrual seizure clustering and two also showed an increased seizure frequency during the luteal phase. In the right hemispheres there was a significant change of CSP duration in the course of the menstrual cycle ($\chi^2 = 8.3$, $P = 0.041$), due to a shorter CSP during the luteal phase ($Z = -2.0$, $P = 0.043$) and menstruation ($Z = -2.2$, $P = 0.028$) as compared to the follicular phase. There was no significant variation of CSP in the left hemispheres. RMT, ICI and ICF showed no significant changes in the course of the menstrual cycle.
Conclusions: The CSP changes suggest a decreased inhibition involving GABA-ergic neurotransmission during the luteal phase and menstruation. These TMS alterations correlated with the clinical course of the epilepsies and were found in the hemispheres containing the majority of the epileptogenic zones.

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Introduction

About one-third of women suffering from epilepsy experience catamenial seizure exacerbation.[1] Results of animal studies suggested that cyclical seizure clustering is caused by fluctuations of female sexual steroids and their effects on the GABA-ergic system.[2–4] The pathophysiology underlying cyclical seizure clusters in human epilepsy is still unclear and only few studies confirmed cyclical changes of GABA-ergic transmission in healthy women.[5,6]

Multiparametric transcranial magnetic stimulation (TMS) offers the opportunity to separately examine excitatory and inhibitory functions of the motor cortex on different days of the menstrual cycle[5] and can, therefore, be used to detect cyclical changes in the excitability of the primary motor area.

In order to explore changes in cortical excitability underlying catamenial seizure exacerbation, we applied multiparametric TMS to patients with catamenial epilepsy during different phases of their menstrual cycle.

Methods

Patients

Over a 2-year period (2004—2005), we included six female epileptic patients in their reproductive age according to the following criteria of eligibility.

Inclusion criteria

(1) Catamenial epilepsy defined as doubling of seizure frequency during one or two of the four cycle phases (follicular phase: day 4 to day 9 (day 1 being the first day of menstrual bleeding); ovulation: day 10 to day −13 (13 days before the onset of the following menstrual bleeding); luteal phase: day −12 to day −4; menstruation: day −3 to day 3 of the following menstrual cycle[1]) as compared to the remaining phases observed at least for the last 12 months.
(2) Active epilepsy defined as at least one seizure per month over the last 6 months.
(3) 18—40 years of age.
(4) Regular menstrual cycle of 25—30 days during the last six cycles.
(5) Right-handedness.

Exclusion criteria

(1) Menstrual-related affective disorders.
(2) Use of hormonal contraceptive methods, pregnancy, lactation period.
(3) Fluctuation of cycle length of more than ±1 day.
(4) History of ovarectomy.
(5) Endocrinological abnormalities (such as hyperthyroidism or hyperandrogenaemia).
(6) Cardiac pacemaker, vagal nerve stimulator or intracranial metal implantates.
(7) History of previous neurosurgery or fracture of the skull.
(8) No change of the anticonvulsant medication for at least 3 months before and during the cycle tested.

All patients provided written informed consent after a detailed explanation of the experimental testing. The study conformed to the standards set by the Declaration of Helsinki and had the approval of the local Ethics Committee.

Estradiol and luteinizing hormone (LH) were tested on day −14, at the assumed time of their peak causing ovulation. Progesterone levels were measured during the luteal phase on day −7. A menstrual cycle was classified as ovulatory when progesterone levels exceeded 5 ng ml^{-1}.[1]

Methods

All patients were investigated on day 8 (follicular phase), day −14 (ovulation), day −7 (luteal phase) and day 2 (menstruation of the following menstrual cycle).[1]

Single- and paired-pulse transcranial magnetic stimulation was delivered through a figure-of-eight shaped magnetic coil following a protocol described in detail elsewhere.[7] The following TMS parameters were evaluated in both hemispheres.

The resting motor threshold (RMT) was defined as the minimal stimulus intensity required to induce a MEP of more than 50 μV peak-to-peak amplitude in a relaxed muscle in at least five out of 10 consecutive trials. Intracortical inhibition (ICI) and facilitation (ICF) were obtained by paired-pulse paradigms at short interstimulus intervals (ISI) of 2 and 3 ms (ICI) and longer interstimulus intervals of 10 and 15 ms (ICF),[7] respectively. The conditioning stimulus was set to an intensity of 75% of RMT, the intensity of the following test stimulus was adjusted to produce MEPs of an approximately 1.5 mV peak-to-peak amplitude at rest. One parameter for ICI was created by averaging the values obtained by ISI 2 and 3 ms for each woman and ICF was defined as the average of the values of ISI 10 and 15 ms.

The cortical silent period (CSP) was measured at a stimulus intensity of 110% of the RMT. The subjects were instructed to hold a voluntary muscle contraction of approximately 30% of the maximal force. The CSP duration was defined as the time interval from

Table 1 Clinical characteristics of patients

Patient	Epilepsy syndrome	Side	Medication	EEG	MRI	Seizure exacerbation
1	TLE	Bilateral	CBZ, LEV, LTG	Bitemporal SP; bitemporal SW	Bilateral HS	Perimenstrual
2	Focal	Unknown	CBZ, VPA	Left temporal IS	Unremarkable	Perimenstrual and ovulatory
3	FLE	Right	CBZ, CLB, LEV, TPM	Right frontal SP; right frontal SW	Unremarkable	Perimenstrual
4	IGE	n.a.	ESM, VPA	Generalized SWC	Unremarkable	Perimenstrual
5	TLE	Right	LTG, VPA	Right temporal SP; bitemporal IV	Unremarkable	Luteal and perimenstrual
6	TLE	Right	LTG, TPM	Right temporal SP; bitemporal SW	Right HS	Luteal and perimenstrual

FLE: frontal lobe epilepsy, IGE: idiopathic generalized epilespy, TLE: temporal lobe epilepsy.
n.a.: not applicable.
ESM: Ethosuximid, CLB: Clobazam, CBZ: Carbamazepine, LEV: Levetiracetam, LTG: Lamotrigine, TPM: Topiramate, VPA: Valproate.
IS: intermittent slow, SP: seizure pattern, SW: sharp waves, SWC: spike and wave complex.
HS: hippocampal sclerosis.

the beginning of the stimulus induced MEP to the first recurrence of voluntary EMG activity.

Statistical analysis

The non-parametric Friedman test for multiple comparisons was used for statistical analysis. Significant results were further analysed using the Wilcoxon signed rank test. In this exploratory study, the level of significance of each comparison was set to $P < 0.05$. Left and right hemispheres were analysed separately.

Results

Six patients with catamenial epilepsy and ovulatory cycles (age: 38.7 ± 7.8 years, cycle length: 28.0 ± 2.2 days, estrogen levels on day -14: 114.7 ± 55.6 pg ml^{-1}, progesterone levels on day -7: 8.3 ± 3.8 ng ml^{-1}) were included. For patient characteristics see Table 1. During the cycle studied, patients 3, 5 and 6 showed their usual course of seizure frequency, patient 1 had four out of eight seizures perimenstrually and patients 2 and 4 were seizure free.

In the right hemispheres there was a significant change of CSP in the course of the menstrual cycle ($\chi^2 = 8.3$, $P = 0.041$), due to a shorter CSP during the luteal phase ($Z = -2.0$, $P = 0.043$) and menstruation ($Z = -2.2$, $P = 0.028$) as compared to the follicular phase (Table 2; Fig. 1). Resting motor threshold ($\chi^2 = 1.3$, $P = 0.73$), ICI ($\chi^2 = 3.4$, $P = 0.33$) and ICF ($\chi^2 = 0.60$, $P = 0.90$) did not show significant changes during the menstrual cycle.

There were no significant changes of any of the TMS-parameters in the left hemispheres (CSP: $\chi^2 = 1.8$, $P = 0.62$; RMT: $\chi^2 = 4.1$, $P = 0.25$; ICI: $\chi^2 = 2.6$, $P = 0.46$; ICF: $\chi^2 = 1.4$, $P = 0.71$; Table 2) and neither comparing the left with right hemispheres for any of the TMS-parameters. Three patients suffered from focal epilepsy with an epi-

Table 2 TMS-parameters in the course of the menstrual cycle

	cycle phase	n	CSP (ms) Median (Quartiles)	RMT (% of MSO) Median (Quartiles)	ICI (% of TR) Median (Quartiles)	ICF (% of TR) Median (Quartiles)
Right hemisphere	day 8	6	212.1 (167.6 – 265.2) ↕	42.0 (38.8 – 54.3)	67.3 (46.8 – 87.9)	118.1 (108.7 – 132.8)
	day -14	6	194.8 (155.7 – 246.8)	47.5 (38.8 – 52.5)	49.9 (20.8 – 83.3)	114.5 (106.7 – 125.7)
	day -7	6	169.5 (156.5 – 243.9) ↕	45.0 (38.8 – 56.0)	48.3 (35.4 – 74.7)	121.0 (94.0 – 179.0)
	day 2	6	190.8 (145.7 – 228.3)	48.0 (39.8 – 51.8)	50.3 (19.0 – 68.0)	128.0 (97.6 – 141.5)
Left hemisphere	day 8	6	197.0 (149.9 – 248.7)	47.0 (39.8 – 55.0)	56.4 (46.4 – 64.4)	130.1 (107.4 – 155.0)
	day -14	6	188.7 (153.0 – 219.8)	44.5 (39.0 – 53.8)	36.2 (28.2 – 59.4)	129.8 (107.1 – 180.3)
	day -7	6	214.3 (145.7 – 231.7)	41.0 (37.5 – 51.8)	32.0 (23.6 – 64.0)	114.0 (93.4 – 135.2)
	day 2	6	180.7 (149.0 – 218.1)	43.5 (40.3 – 57.8)	36.1 (27.3 – 65.2)	130.1 (86.6 – 170.3)

CSP: cortical silent period; RMT: resting motor threshold; ICI: intracortical inhibition; ICF: intracortical facilitation; MSO: maximal stimulator output; TR: test response.
↕: $P < 0.05$.

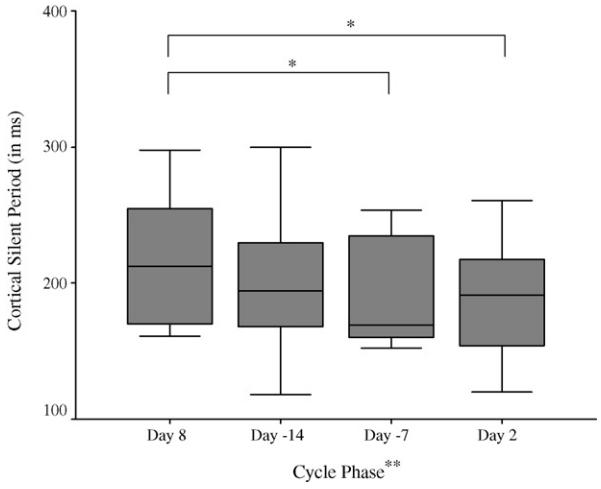

Figure 1 Duration of the cortical silent period (in ms) in the course of the menstrual cycle; Line: median, boxes: 25—75% quartiles, whisker: maximum and minimum, (*) $P < 0.05$, (**) Friedman test: $\chi^2 = 8.3$, $P = 0.041$.

leptogenic zone restricted to one hemisphere (patients 3, 5 and 6). The median (range) of the CSP in the ipsilateral, right hemispheres was lower as compared to the contralateral, left hemispheres at all four testings with a maximal difference at day −7 (ipsilateral: day 8: 170 ms (161—254 ms), day −14: 175 ms (168—215 ms), day −7: 160 ms (153—169 ms), day 2: 154 ms (120—215 ms); contralateral: day 8: 189 ms (112—259 ms), day −14: 192 ms (154—227 ms), day −7: 211 ms (129—222 ms), day 2: 163 ms (106—232 ms)).

Discussion

In the present study, the excitability of the motor cortex was assessed by TMS during ovulatory cycles in patients with catamenial epilepsy. Only women with stable cycles were included to obtain a homogeneous patient group. The cortical silent period was shortened during the luteal phase and menstruation as compared to the follicular phase. This correlated well with the history of perimenstrual seizure clustering in all and luteal seizure clustering in two of the six patients included in this study.

In four of the six patients, the right hemisphere harboured the epileptogenic zone[8] in whole or in part. In contrast, only one patient may have had the epileptogenic zone exclusively in the left hemisphere (patient with focal epilepsy of unknown origin). The CSP alteration was observed only in patients' right but not in the left hemispheres. There is evidence that focal epilepsies influence chronically the ipsilateral motor cortex, leading to a decreased inhibition seen as shortened CSP even when the epileptogenic zone is apart from it.[7,9] This alteration was attributed to synaptic reorganization involving $GABA_B$-ergic neurotransmission. It can be hypothesized from the present results that ipsilateral cortex altered by focal epilepsies responds differently to cyclical hormonal fluctuations as compared to unaffected contralateral cortex, hence facilitating catamenial changes in seizure threshold. This could explain the finding that the CSP alteration in the present study was seen in right hemispheres only, which contained the majority of the focal epilepsies and the active focus of all patients who showed their usual catamenial seizure exacerbation during the cycle studied.

Hormonal effects

In animal studies, estrogens were reported to increase and progesterone to inhibit cortical excitability and cause cyclical changes in seizure susceptibility.[2—4] It remained unclear whether these results are the cause of the cyclical changes in human epilepsy.

As compared to the follicular phase, our results showed a shorter CSP during the luteal phase, when both estrogen and progesterone levels are elevated.[1] This supports the view of an excitatory effect of estrogens on cortical excitability. The decreased progesterone to estradiol ratio found in patients with epilepsy may also play a role.[10,11] The decrease in CSP during menstruation may be caused by falling progesterone levels.[1] Even though estrogen levels peak before ovulation, there was no significant shortening of the silent period at ovulation. This may be due to the short duration of the estrogen peak,[1] which has possibly been missed at our testing on day −14 (ovulation) in some of the patients, as suggested by the relatively low serum estrogen levels in this study.[1] Reflecting the unchanged CSP at ovulation, it is noteworthy that only one woman in the present study showed periovulatory seizure clustering.

Conclusions

The results of the present TMS study on women with catamenial epilepsy revealed a shortened CSP during the luteal phase and menstruation which correlated well with the clinical course of the catamenial epilepsies included. The CSP alterations were found in the hemispheres which contained the majority of the epileptogenic zones. This may indicate an altered responsiveness of GABA-ergic transmission

to sexual hormones in epileptic hemispheres leading to cyclical changes in seizure threshold.

Future studies on larger patients groups with more homogeneous epilepsy syndromes are warranted.

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