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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