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# New perspectives in the course of treatment of catamenial epilepsy

**Short title:** Management of catamenial epilepsy treatment

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***Abstract---Background.****Catamenial epilepsy occurs in 5% of all women suffering from epilepsy. Here, the appearance of epileptic seizures is facilitated by hormonal disorders (changes in the ratio of estrogens/progesterone), violations of the water-electrolyte balance, a decrease in the level of antiepileptic drugs in the blood, premenstrual stress. During cyclic changes occurring in the ovaries, a statistically significant positive equivalence between estradiol and progesterone in serum was revealed. Premenstrual exacerbation of seizures was associated with the rapid extinction of the anticonvulsant action of progesterone. According to studies in female animal models, progesterone has been found to inhibit neuronal arousal and reduce spontaneous epileptic discharges. Ovariectomy in adult female rats is tantamount to a menopausal condition, and has been associated with increased convulsive activity. These rats showed faster progression of epileptic status compared to intact animals.* ***The aim of this study*** *is to present preclinical and clinical data on the relationship between female reproductive steroids and epileptic seizures, and to describe approaches to the treatment of catamenial epilepsy. In our study, we recommend monotherapy – topiramate, in order to reduce the risk of teratogenic effects on the fetus, in case of pregnancy.*

***Material and methods:*** *The study included 60 women with catamenial epilepsy (CE). The control group consisted of 20 women with symptomatic epilepsy that did not have a cyclic course. We studied the fluctuation of women sex hormones in women with catamenial epilepsy in the follicular and luteal phases of the cycle. The study of the dynamics of changes was based on the assessment of menstruation and seizures for at least two cycles. The number of attacks in each phase was counted.*

***Results:*** *As our studies have shown, fluctuations in estrogen and progesterone are noted in the follicular phase of the menstrual cycle. To optimize therapy, we replaced the anticonvulsant drug Carbamazepine with topiramate at the rate of 3-5 mg / kg body weight per day. Moreover, the average daily dose did not exceed 200 mg / day. The duration of monitoring the effectiveness of therapy was 6 months. Over this period, we noted a positive trend during catamenial epilepsy, which was expressed in a decrease in the frequency and duration of seizures, and in 28% of cases we noted a state of clinical remission, i.e. no attacks were observed during the observation period.*

***Key words---****catamenial epilepsy, estrogen, progesterone, ovariectomy, topiramate.*

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# I. INTRODUCTION

Issues of epilepsy in women is a problem of exceptional importance, which is associated not only with the course of the disease itself, but also with the effect of antiepileptic drugs (AEDs) on the reproductive health of women, with the realization primarily of the maternal function of women suffering from epilepsy[4]. In the 80-90 years XX century Clinical-EEG-hormonal features of catamenial epilepsy, specificity of clinical manifestations, course, pathogenetic mechanisms of epilepsy in women are described, approaches to the treatment of epilepsy taking into account age-gender characteristics are developed[5].

Epilepsy in women is characterized by problems associated with epilepsy as a disease, as well as problems associated with the reproductive function of women[1,3,6]. In particular, these are the features of the menstrual cycle, catamenial dependence of seizures, sexual development, contraception, fertility, pregnancy and childbirth, lactation, menopause. The difficulties of curating patients with epilepsy are that during treatment it is necessary to take into account the whole range of these problems.

When choosing a treatment strategy for women with epilepsy, the effect of antiepileptic drugs (AEDs) on the reproductive system should also be considered. AEDs are known to induce the production of sex hormones by inducing and or inhibiting microsomal liver enzymes. This ultimately affects the harmonic balance, in particular the progesterone / estrogen ratio and aggravates the course of epilepsy[7].

According to most researchers, among women with epilepsy, reproductive endocrine disorders are more common than in the general population. They include: menstrual irregularities, hyperprolactinemia, hyperandrogenism, sclerocystic ovaries, polycystic ovary syndrome and others[2,8]. Various mechanisms of these harmonic disturbances are considered. However, discussions are still ongoing about the extent to which the disease itself affects the hypothalamic-pituitary-ovarian system, causing reproductive disorders, and what is the role of antiepileptic drugs in the development of these disorders[9]. It has been shown that epilepsy and antiepileptic drugs can have a complex effect on the reproductive system, leading to a decrease in fertility in both women and men. The studied literature describes the effect of estrogen and progesterone levels on the course and frequency of epileptic seizures[10]. At the same time, estrogen has a proconvulsive effect, and progesterone has an anticonvulsant effect. However, we did not meet the works devoted to the study of the influence of the degree of hyperestrogenemia on the development and course of CE[11]. In this connection, the aim of our study was to study the neuroendocrine factors in the development of catamenial epilepsy.

**Objective**

to optimize the treatment of catamenial epilepsy by studying neuroendocrine factors. Find the most effective and harmless therapy that meets the requirements.

# II. MATERIAL AND RESEARCH METHODS

The study included 60 women with catamenial epilepsy (CE). The comparison group consisted of 20 women with symptomatic epilepsy, independent of the menstrual cycle. The study of patients included clinical, medical, neurological, neurophysiological studies, as well as biochemical blood tests. We carried out hormonal studies (estradiol and progesterone) by the enzyme immunoassay in the biochemical laboratory of the Rad Laboratories clinic during the menstrual cycle: in the follicular and luteal phases in 80 patients.

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From 60 patients with catamenial epilepsy, we identified 20 patients (group I) with a resistant form, i.e. the frequency of seizures was 2 times or more per week and could not be corrected both for mono- and duotherapy of AEDs. The second group consisted of 40 patients in whom the administration of AED led to a partial remission of the disease. All 60 patients received carbamazepine as an anticonvulsant therapy, which was prescribed both as mono- and duotherapy at a dose of 10 mg / kg body weight for a period of more than 3 years. The choice of the drug carbamazepine was dictated by the clinical manifestations of catamenial epilepsy.

## III. RESULTS AND DISCUSSION

An anamnestic study revealed in 80% of cases an early menarche with frequent cycle disorders in the form of delays and irregular cycles. Among the etiological factors in the development of CE in our observations prevailed: perinatal pathology - 52% (31 patients), hereditary burden - 63.3% (38 patients), suffered craniocerebral injuries - 10% (6 patients), and less often the cause of development was complications of neuroinfection - 6.7% (4 patients).

The frequency of seizures was observed in patients with frequent seizures (2 or more per week) - 20, rare (less than 5 per month) - 22, single (less than 1 per week) - 18. Among the examined patients of the main group, early manifestation of epilepsy (14-16 years) noted 43 patients. Seizures in patients were both generalized and partial.

To identify the relationship between the level of sex hormones during catamenial epilepsy, we studied estradiol and progesterone in the follicular and luteal phases of the menstrual cycle (Table 1).

**Table 1.** Baseline hormone levels in patients with CE

| Cycle phase | Hormones | Comparison Group (n = 20) | I group (n = 20) | P | II group (n=40) | P |
|---|---|---|---|---|---|---|
| Follicular | estradiol pg/ml | 37,4±4,9 | 67,2±4,8 | <0,001 | 58,3±6,4 | >0,005 |
| | progesterone ng/ml | 0,8±0,04 | 0,8±0,2 | >0,05 | 0,6±0,02 | >0,05 |
| | PG/E | 0,012±0,008 | 0,021±0,004 | >0,05 | 0,010±0,003 | >0,05 |
| Lutein | estradiol pg/ml | 62,6±4,0 | 108,2±5,1 | <0,001 | 88,1±6,4 | <0,01 |
| | progesterone ng/ml | 6,4±1,1 | 18,4±1,1 | <0,001 | 7,6±1,2 | <0,001 |
| | PG/E | 0,10±0,27 | 0,17±0,02 | >0,05 | 0,086±0,18 | <0,001 |

The coincidence of epilepsy attacks with different phases of the menstrual cycle was noted in 100% of cases of the main group. As our studies have shown, fluctuations in estrogen and progesterone are observed in the follicular phase of the menstrual cycle. But in patients with a resistant form of epilepsy, we noted a significant difference in the estradiol indices in group I patients in the follicular phase (67.2±4.8 pg/ml, versus 37.4±4.9 pg / ml in the comparison group), and greater dynamics of increased estradiol in patients of group I compared with group II (108.2±5.1 pg/ml, 58.3±6.4 at control values, 62.6±4.0 pg/ml) into luteal phase. In our opinion, the worst dynamics of estradiol in patients with a pharmacoresistant form of CE indicates a negative effect of AED on the enzyme system of the liver, as well as the need to

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transfer to another type or type of anticonvulsant therapy. There are a number of opinions on the negative effect of this AED on the liver enzyme system, according to which, this may be the reason for the aggravation of the clinical picture of epilepsy (cases with CE are not described).

In order to optimize therapy, we replaced the anticonvulsant drug Carbamazepine with Topepsil at the rate of 3-5 mg / kg body weight per day. Moreover, the average daily dose did not exceed 200 mg/day. The duration of monitoring the effectiveness of therapy was 6 months. Over this period, we noted a positive trend during CE, which was expressed in a decrease in the frequency and duration of seizures, and in 28% of cases we noted a state of clinical remission, i.e. no attacks were observed during the observation period.

Only a small fraction of TPM is metabolized, and up to 40% of the oral dose is eliminated invariably through kidney. Thus, pregnancy-related increase renal blood flow can lead to kidney enlargement clearance and decrease of TM concentration in blood serum[12].

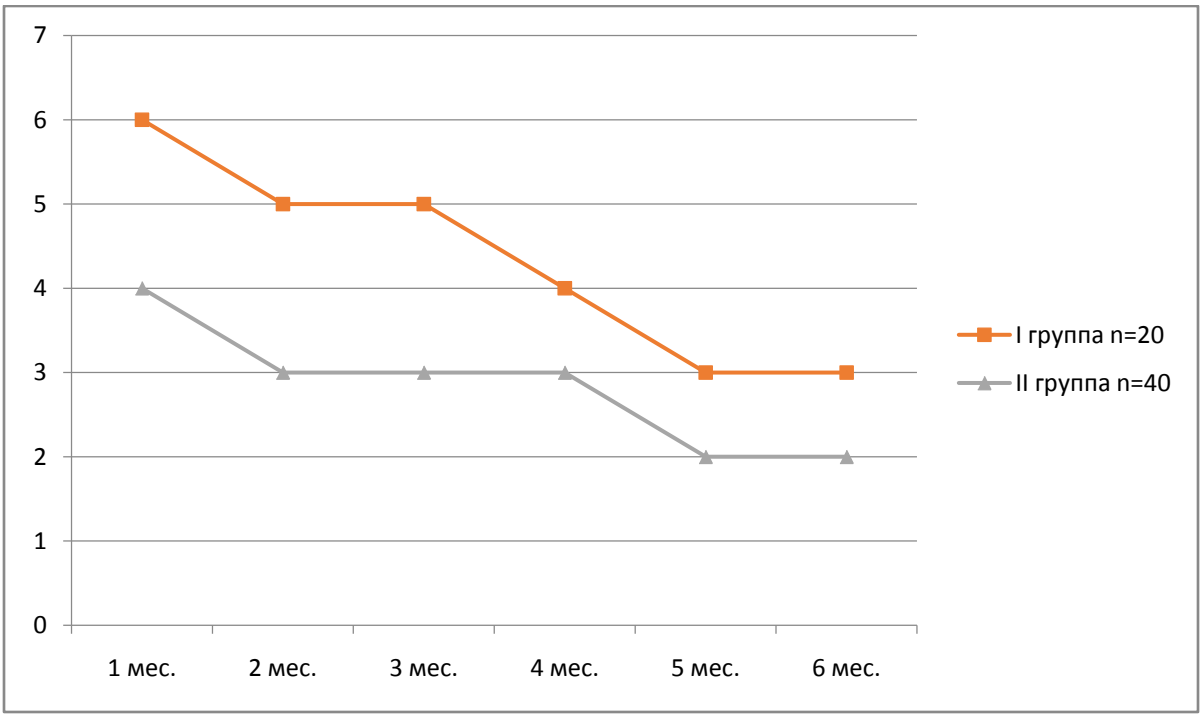


**Fig. 1**. The dynamics of seizures in the examined patients during therapy with Topepsil

An analysis of the level of progesterone and estardiol in the blood of the examined patients showed that, against the background of our topiramate therapy, a significant decrease in the frequency of seizures was noted (Fig. 1). After 6 months of regular administration of topepsil at a dosage of 200 mg / day. in the first group of patients there was a decrease in the frequency of seizures from 2 times a week to 5 seizures per month. At the same time, it is important to note that the dynamics of seizures was the best for 3-5 months of taking topepsil, and reached up to 3 seizures per month by 5 months, and at 6 months of treatment the seizure frequency reached 2 times a month.

In the second group, we also noted a decrease in the frequency of seizures to 1 time per month, however, the dynamics was lower than in the first group. Already by the month of taking topepsil, achievement of the level of 3 seizures per month was noted, but only by 5 months. we noted a decrease in the frequency of seizures up to 2 times per month. In

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addition, patients noted a decrease in the duration of seizures to 1 minute, with baseline values to 3-5 minutes. That is, the seizures underwent changes, both in duration and severity of the course.

When studying the level of hormones, such a positive dynamics in the clinical course was confirmed in the form of an equalization of the progesterone / estrogen ratio (Table 2).

From table 2 it is seen that the use of topiramates led to a decrease in the pathological level of estrogens and an increase in progesterone levels, both in the follicular and luteal phases of the menstrual cycle. At the same time, we noted a significant equalization of the progesterone / estradiol ratio in all phases and in both groups of patients. So in the follicular phase after treatment, this ratio reached control values in both patients of the first group ($0.012 \pm 0.004$ and $0.012 \pm 0.006$, respectively), and in patients of the second ($0.012 \pm 0.004$ and $0.009 \pm 0.003$).

The changes in the ratio of hormones described above are associated, in our opinion, not only with the peculiarity of the mechanism of therapeutic action of topepsil. According to the literature, topiramates do not affect the microsomal enzyme system of the liver, which indirectly inhibits the synthesis of progesterone and induces the synthesis of estradiol. The latter, as you know, has a proconvulsive effect.

Thus, our studies of changes in hormonal status revealed fluctuations in the follicular and luteal phases, which underwent positive changes while taking topepsil. Against the background of taking topepsil in a group of patients with a resistant course, the estradiol indices initially had large values. At the same time, our studies revealed a decrease in progesterone. The progesterone / estradiol ratio in group I patients was higher than in group II.

That is the progesterone / estradiol ratio has priority in predicting the course of CE. Against the background of 6 months of topiramate therapy, we noted a decrease in the ratio of progesterone/estradiol, which was close to that of the control group. This allows reconnecting Topepsil device in the treatment of catamenial epilepsy.

## IV. Conclusions

Epileptic seizures in menstrual epilepsy often begin during puberty, and are usually immediately dependent on the menstrual cycle. With polytherapy, the risks of teratogenic effects of drugs on the fetus are high, so it is necessary to reduce to a minimum the number of drugs taken, preferably to monotherapy. In some cases, with complete control of seizures, you can cancel the drugs completely. In the background we conducted therapy within 6 months there was a significant reduction in the frequency of seizures in patients receiving topiramate. In addition, taking topiramate led to a decrease in pathological estrogen levels and increased progesterone levels, both in the follicular and luteal phases of the menstrual cycle

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**AUTHORS' CONTRIBUTIONS**

This work was carried out in collaboration between all authors. Author GIS designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author FLA and BSA managed the literature searches and manuscript editing. Author NJE did the manuscript review. All authors read and approved the final manuscript.

**CONFLICT OF INTERESTS**

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**ETHICAL APPROVAL**

All authors hereby declare that all investigations have been examined and approved by the appropriate ethics committee (Ethical Committee under the supervision of Ministry of Healthcare, Republic of Uzbekistan) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki updated version adopted by the WMA General Assembly, in 2008.

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