Review article

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CATAMENIAL EPILEPSY- UPDATE ON PRACTICAL MANAGEMENT

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Catamenial epilepsy is a type of epilepsy that is characterized by aggravation and seizures clustering in a perimenstrual or periovulatory periods. Neuroactive properties of reproductive steroids and cyclic variations in their concentrations are important pathophysiological factors. Recent researches have demonstrated and confirmed the presence of at least three forms of catamenial aggravation of the attacks: perimenstrual and periovulatory in ovulation cycles and pattern throughout the whole luteal phase in anovulatory cycles. Rational models have identified that approximately one-third of women with epilepsy may have catamenial aggravation of the seizures. Open studies using cyclic natural progesterone as add-on therapy, medroxyprogesterone and gonadotropin-releasing hormone analogues have shown therapeutic benefits in certain forms of catamenial epilepsy. Therefore, it is important for the physician to consider catamenial epilepsy as a common type of epilepsy in women and recognize a particular pattern of this condition with the potential for good therapeutic response.

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Key words: *epilepsy, reproductive hormones, seizure clustering, menstruation*

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Introduction

The term catamenial epilepsy refers to the aggravation of attacks during the various stages of the menstrual cycle in women with epilepsy. Catamenial epilepsy occurs in one-third to one half of women with epilepsy (1, 2) and is described in almost one-third of women with pharmacoresistent focal epilepsy (3). The basic principles have been described in the previous publications of the Yugoslav Union of Leagues Against Epilepsy (4, 5), and the aim of this paper is to make a brief overview of the latest achievements in this area.

Endogenic hormons and catamential epilepsy

It has long been known that estradiol has a provocative effect that makes women more susceptible to the seizures. On the contrary, progesterone and some of its metabolites reduce the incidence of epileptic attacks in women with epilepsy, which is associated with its anticonvulsant effects. Therefore, catamenial epilepsy may result from decrease in progesterone levels and/or a relative increase in estradiol/progesterone ratio (6).

In women with normal menstrual cycles, the most significant hormonal variations for catamenial exacerbation of the attack are the onset of a fast estrogen pulse on the 13th day (which induces ovulation) and a rapid drop in progesterone and estrogen from 26 to 28 days, just before the onset of menstrual bleeding.

The most common forms of catamenial epilepsy are:

1) *The perimenstructural pattern (C1)* is the most common form of catamenial epilepsy and is defined as maximum frequency of attacks during the menstrual phase (from the 25th day of the cycle to the third day of the next cycle). This pattern relates to decline in progesterone in perimenstrual periods.

2) *The periovulatory pattern (C2)* is the second most frequently observed pattern and is characterized by the maximum occurrence of attacks during ovulation (10-15 days). This form correlates with a rapid increase of estrogen in mid phase of ovulations.

3) *Luteal pattern (C3)* is characterized by the maximum frequency of attacks during ovulatory, middle luteal and menstrual phase (day 10 to day 3 of the next cycle), compared to the frequency of attacks in the middle follicular phases (3-10 days) in cycles with inadequate luteal phase. This is the third most commonly observed pattern and associates with a low level of progesterone seen in anovulatory cycles.

These three most frequent patterns of catamenial attacks have been confirmed in several studies. El-Khayat et al. described the case of women with catamenial attacks that correlate with a reduction in progesterone levels (7). Quite the opposite, another study pointed to variations in estrogen concentrations as an indicator of catamenial attacks, with no significant changes in progesterone levels (8). Several other studies have indicated the importance of the hormone changes in the onset and cyclical patterns of seizures, including anovulatory cycles in women with epilepsy (9-11). Therefore, both estrogen and progesterone are involved in mechanisms of catamenial epilepsy.

Furthermore, recent clinical studies have shown that women with catamenial epilepsy have better control of attacks during pregnancy, which is probably a consequence to the absence of cyclical hormone variations and the increase in circulating progesterone levels (12).

Specific animal models of catamenial epilepsy have been developed (13). They also approve the significance of neurosteroids in pathophysiological mechanisms.

The effects of neurosteroids that bring out the onset of catamenial epilepsy attacks include:

- premenstrual decline of anticonvulsant effects of neurosteroids via action on GABA-A receptors,
- alteration of the GABA-A receptor subunit and consequent changes in neural inhibition
- sudden peak of estrogen in days before ovulation and
- an increase in the frequency of anovulatory cycles due to the deregulation of the hypothalamic-pituitary-gonadal axis and, subsequently the luteal phase with a low progesterone level.

For example, the experimental model of catamenial epilepsy developed in female rats by hippocampal kindling method, points to the following mechanisms as the key to the onset of catamenial attacks: the premenstrual reduction of progesterone combined with plasticity and changes in GABA-A receptor function during menstrual phase (perimenstrual in humans) leads to exacerbation of seizures (13).

Treatment

Hormonal therapy

The majority of hormonal treatments for catamenial epilepsy involved add-on therapy with natural progesterone, synthetic forms of progesterone or therapy based on menstrual cycle suppression.

The degradation of natural progesterone to allopregnanolone, a neurosteroide with anticonvulsant effects, provides a potential therapeutic option for controlling the attacks. Two small, open studies evaluated natural progesterone as add-on treatment in women with complex partial seizures (14, 15). A study with a long-term follow-up (16) suggests that the use of natural progesterone, in the form of vaginal suppositories or oral lozenges, starting at the time of ovulation (day 14) to the beginning of the next cycle, is an effective treatment for catamenial epilepsy.

A randomized, double-blind, placebo-controlled multicenter study evaluated progesterone treatment in the form of 200 mg oral lozenges twice a day from 14^{th}-28^{th} day of the cycle (11). The positive response, defined as 50% or more reduction of seizures, did not differ between the progesterone and placebo groups when all patients were analyzed, or when comparing patients with or without catamenial epilepsy.

However, the secondary analysis indicated that the perimenstrual (C1) pattern of catamenial epilepsy is a predictor for the response to progesterone. If a woman has three or more times frequent seizures during the C1 phase (days -3 to +3) compared to other days of cycles, then 37.8% have a positive therapeutic response to progesterone while it was case in only 11.1% of patients in the placebo group. For women who have eight or more times frequent seizures during the C1 phase, almost 70% of them will have a good therapeutic response to progesterone. These results suggest that the degree of perimenstrual pattern of the attacks (C1 pattern) is a significant predictor for the response to progesterone therapy. Evidence supporting the efficacy of progesterone in patients with C1 type of attack suggests that benefits increase as the period of perimenstrual occurrence of attacks is shorter and closer to perimenstrual days. These results are in accordance with molecular and *in vivo* models (13, 17, 18). However, this hypothesis also points that catamenial worsening of attacks during the ovulation period cannot be effectively treated with progesterone.

Medroxyprogesterone acetate is a synthetic progesterone, usually used as contraceptive agent. The mechanism of its effect on reducing the seizures is unclear, but it is believed to be connected to interruption of cyclic variations in estrogen and progesterone levels. In patients with catamenial epilepsy, the use of medroxyprogesterone acetate was associated with a reduction in seizure frequency of 39% after one year of follow-up (19, 20).

Medroxyprogesterone acetate is administered in the form of an intramuscular injection and stops the regular menstrual cycle. The standard dose is 150 mg i.m. every 12 weeks. Some clinicians propose a dosing frequency every 10 weeks in order to reduce the risk of interaction with inductor AEDs. Additionally, medroxyprogesterone acetate is associated with higher risk of osteoporosis, as well as with therapy with inductor AEDs (21). Moreover, beyond cessation the medroxyprogesterone acetate therapy, endogenous hormones can vary significantly over the next few months, which can lead to worsening of the seizure control and a prolong period for return to normal fertility.

Some clinicians use a strategy to inhibit normal cyclic release of reproductive hormones by using continuous oral contraceptive pills that suppress ovu-

lation. So far, there is no data on the effectiveness of this strategy from controlled clinical studies.

Non-hormonal therapy

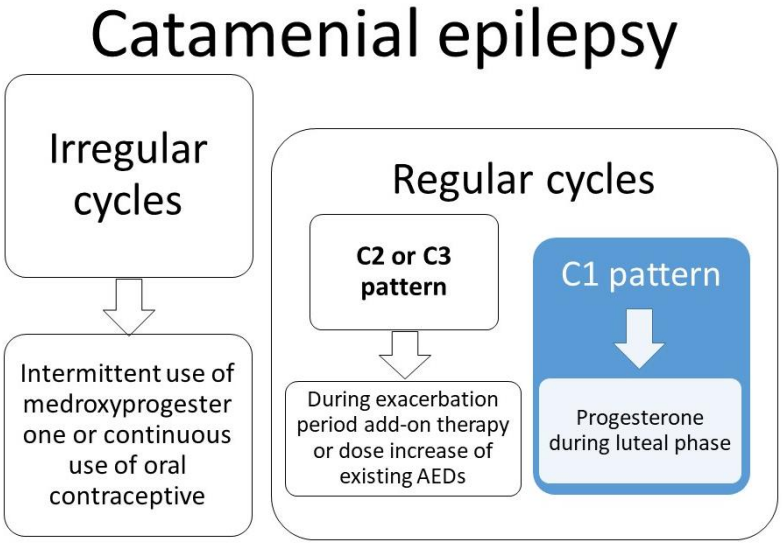
Most non-hormonal based medications were evaluated in the premenstrual (C1) pattern of catamenial epilepsy. Women with regular menstrual cycles are good candidates for these interventions, because medication must be taken a specific number of days after the onset of menstrual bleeding. Generally, treatment starts at some point during the second phase of the cycle (14^{th}-26^{th} day), depending on the individual form of the seizures, bearing in mind that the luteal phase lasts 14 days.

Acetazolamide is used to treat catamenial epilepsy for 60 years (22), although it has never been evaluated in randomized studies. Doses of 250-500 mg per day have been effective when administered 3-7 days before the start of the cycle (22, 23).

Benzodiazepines were used mainly for cessation of seizure clusters but were administered intermittently due to the risk of habituation and/or tolerance during chronic use. Clobazam is the only benzodiazepine which is formally evaluated for the treatment of catamenial epilepsy. In a double-blind, placebo-controlled, cross-sectional study, clobazam was associated with better control of the attack than placebo. Complete control of attacks was observed in most patients during the 10-day treatment (24).

Temporarily increasing the dose of existing AED therapy at the specific time during the menstrual cycle is another rational option. It is an empirical approach, although phenytoin should not be increased due to the risk of toxic effects associated with its non-linear kinetics.

Summary of therapeutic strategies for catamenial epilepsy is presented on Figure 1.



AED- Antiepileptic drugs;
C1- Perimenstrual pattern of catamenial epilepsy;
C2- Periovulatory pattern of catamenial epilepsy;
C3- Luteal pattern of catamenial epilepsy.
(For more details see text)

Figure 1. Summary of therapeutic strategies for catamenial epilepsy

Conclusion

As with most therapeutic approaches for treatment of epilepsy, there are no medication that fits for all patients. Adequate analysis of frequency and time of occurrence of attacks is the key to understanding pathophysiological mechanisms and the implementation of adequate therapy. In women with a clear perimenstrual pattern of seizures, the possibility of using natural forms of progesterone should be considered, with the initiation of treatment in accordance to the anticipated period of aggravation of the attacks. Therapeutic strategies must be made in agreement with the patient in terms of considering potential adverse effects of increasing existing therapy or short-term use of benzodiazepines or acetazolamide. Women with irregular cycles are probably not good candidates for intermittent interventions; they should consider options for therapy based on suppression of menstrual cycles, after discussing long-term consequences and side effects.

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KATAMENIJALNA EPILEPSIJA- NOVINE U LEČENJU

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Katamenijalna epilepsija predstavlja tip epilepsije koja se karakteriše pogoršanjem i grupisanjem napada u perimenstrualnom ili periovulatornom periodu. Neuroaktivna svojstva reproduktivnih steroida i ciklična varijacija u njihovim koncentracijama važni su patofiziološki faktori. Najnovija istraživanja su pokazala i potvrdila postojanje najmanje tri obrasca katamenijalnog pogoršanja napada: perimenstrualno i periovulatorno kod ovulatornih ciklusa i obrazac tokom cele lutealne faze kod anovulatornih ciklusa. Racionalni modeli su identifikovali da približno jedna trećina žena sa epilepsijom može imati katamenijalno pogoršanje napada. Otvorene studije koje su koristile ciklično dodavanje prirodnih progesteronskih preparata, depo medrokiprogesteron i analoge gonadotropin-oslobađajućeg hormona pokazale su terapijske benefite kod određenih formi katamenijalne epilepsije. Stoga je važno da lekar ima na umu katamenijalnu epilepsiju kao česti oblik epilepsije kod žena i da prepozna specifične kliničke obrasce koji mogu imati dobar terapijski odgovor.

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Ključne reči: *epilepsija, reproduktivni hormoni, grupisanje napada, menstruacija*