

# Diagnosis and management of catamenial seizures: a review

Alberto Verrotti<sup>1</sup>  
Claudia D'Egidio<sup>1</sup>  
Sergio Agostinelli<sup>1</sup>  
Carla Verrotti<sup>2</sup>  
Piero Pavone<sup>3</sup>

<sup>1</sup>Department of Paediatrics, University of Chieti, <sup>2</sup>Department of Obstetrics and Gynecology, University of Parma, <sup>3</sup>Unit of Paediatrics, University Hospital "Vittorio Emanuele", Catania, Italy

**Abstract:** Catamenial epilepsy is defined as a pattern of seizures that changes in severity during particular phases of the menstrual cycle, wherein estrogens are proconvulsant, increasing the neuronal excitability; and progesterone is anticonvulsant, enhancing GABA-mediated inhibition. Thus, changes in serum estradiol/progesterone ratio throughout a normal reproductive cycle bring about an increased or decreased risk of seizure occurrence. To date, there are no specific drug treatments for catamenial epilepsy however, non-hormonal and hormonal therapies have been proposed. The aim of this review is to report preclinical and clinical evidences about the relationship between female reproductive steroids and epileptic seizures, and to describe treatment approaches for catamenial epilepsy.

**Keywords:** catamenial epilepsy, estrogens, progesterone, neurosteroids

## Introduction

Women with epilepsy may have seizure patterns associated with changes in estrogen and progesterone levels.<sup>1</sup> In fact, estrogen and progesterone have been shown to have effects on neuronal excitability.<sup>2,3</sup>

In catamenial epilepsy seizures tend to cluster in relation to the menstrual cycle;<sup>4</sup> this may be construed as a greater increase in seizure frequency during a particular phase of the menstrual cycle.<sup>5</sup>

Catamenial seizures can affect from 10% to 70% of fertile women with epilepsy.<sup>6-8</sup> This wide variability in prevalence of catamenial epilepsy may be due to the different criteria used for defining seizure exacerbation associated with the menstrual cycle including, patients self-reporting, diaries, and other inaccurate records of seizures relating to menses.<sup>6,8-11</sup>

Knowledge of the effects of sex hormones on epilepsy may open new therapeutic approaches, in addition to antiepileptic drugs, for women with catamenial seizures pattern.

## Relationship between epilepsy and the menstrual cycle

Catamenial epilepsy is believed to occur secondarily to the neuroactive properties of endogenous steroid hormones and the natural cyclic variation in their serum levels throughout the menstrual cycle.<sup>4</sup>

Herzog<sup>4</sup> distinguished three patterns of catamenial seizure exacerbation, relating to the higher seizure occurrence during the specific phases of the menstrual

Correspondence: Claudia D'Egidio  
Department of Paediatrics,  
University of Chieti, Hospital  
"Policlinico SS Annunziata,  
Via dei Vestini 5, 66100 Chieti, Italy  
Tel +39 09871 358 015  
Fax +39 0871 574 831  
Email claudia.degidio@hotmail.it

cycle: the perimenstrual, periovulatory, and inadequate luteal phase patterns.

In ovulatory cycles, the higher ratio of serum estradiol/progesterone during the premenstrual period has been shown to lead to the clustering of seizures. Probably, the sudden withdrawal of progesterone, analogous to a benzodiazepine withdrawal, could be the cause of the premenstrual rise in seizure frequency, while, during the days preceding ovulation, the rapid and steep rise in serum estradiol concentration is believed to be responsible for the increase of seizures at that time.<sup>11</sup> Seizures are least likely to occur during the mid-luteal phase, during which the serum progesterone levels are higher than those of serum estradiol.<sup>12,13</sup>

In women with anovulatory cycle, in which luteal phase is characterized by low levels of progesterone, seizure frequency increases in the premenstrual phase because the mid cycle surge in estrogen still occurs, without a significant increase in progesterone levels.<sup>11,14,15</sup> Anovulatory cycles can occur even in women with regular menstrual cycles, although the number of anovulatory cycles increases with cycle length. Approximately 10% of menstrual cycles in healthy women are anovulatory, whereas 35% are anovulatory in women with temporal lobe epilepsy.<sup>16,17</sup> Thus, for up to 4 months a year, it is possible that woman may experience this third, nonspecific seizure pattern, which obscures recognition of catamenial epilepsy.<sup>16</sup>

Interestingly, some studies have shown that catamenial epilepsy is substantially and statistically significantly more common among women with left temporal foci than among those with right temporal foci.<sup>18,19</sup> These findings suggest that circa lunar rhythms of seizures in women, and therefore possibly also strategies of hormonal treatments for catamenial epilepsy, vary with the neuroanatomic substrate of the seizure focus. Furthermore, Quigg et al<sup>19</sup> also reported that age affects overall seizure rate: youth increases seizure occurrence across the 28-day cycle. Because this factor is phase-independent, the modulatory effect of age may arise from factors outside the cyclic effects of the hypothalamic-pituitary-gonadal axis.

## Pathophysiology of catamenial epilepsy

It is known that estrogen and progesterone have important effects on neuronal development and plasticity in widespread cerebral and brainstem regions,<sup>20</sup> through their capacity to regulate synthesis, release, and transport of neurotransmitters.<sup>21</sup>

## Effects of estrogens

Estrogens have proconvulsant and epileptogenic properties in animals and humans. There are also studies that support protective effects of estrogen and that suggest that it may also be anticonvulsant under some circumstances.<sup>27</sup>

In animal models, the thresholds of limbic seizures in female rats are inversely related to estradiol levels,<sup>22</sup> and intravenous or topical administration of estradiol in rabbits increases spontaneous electrically recorded paroxysmal spike discharges.<sup>23</sup> However, in a study by Terasawa and Timiras, the threshold for seizures decreased in the hippocampus but increased in the amygdala during the regular cycle.<sup>22</sup>

The mechanism by which estradiol increases neuronal excitability is not clearly understood; however, in experimental studies, there are many factors influencing effects of estrogen on seizure susceptibility, such as sex, age, the hormone species (natural or synthetic), regional distribution of hormone receptors, treatment duration, time interval for initiation of hormonal treatment following gonadal removal, route of administration, as well as the dose.

There are two different estrogen receptors, ER $\alpha$  and ER $\beta$ , through which estrogens determine their biological effects.<sup>5</sup> Estradiol is able to modulate the plasticity of axonal terminals, increasing the number of dendritic spines of the hippocampal CA1 pyramidal neurons and the production of mRNA for N-methyl-D-aspartate (NMDA) receptor subunits, as well as the density of excitatory NMDA receptors on the dendritic spines: NMDA-mediated calcium entry increases with a larger amount of excitatory inputs to the pyramidal cells.<sup>24,25</sup> Another possible mechanism is that estradiol causes a down-regulation of glutamic acid decarboxylase, the enzyme that mediates glutamate conversion to gamma-aminobutyric acid (GABA), in ovariectomized rats.<sup>26</sup> Thus in animal models, exposure to estradiol possibly facilitates excitatory neurotransmission in regions that are important in seizure vulnerability.

Notably, Osborne and Frye<sup>27</sup> have suggested that estrogen may also have antiseizure effects, by elevating the level of 5 $\alpha$ -pregnan-3 $\alpha$  ol-20-one (3 $\alpha$ , 5 $\alpha$ -THP), a metabolite of progesterone, in the hippocampus. To test this hypothesis, castrated or ovariectomized, wild-type and 5 $\alpha$ -reductase knockout mice were implanted with Silastic capsules of estradiol, and then administered pentylentetrazol (85 mg/kg, intraperitoneal injection). Wild-type, but not 5 $\alpha$ -reductase knockout, rats that were administered estradiol had significantly longer latencies to myoclonus and increased levels of 3 $\alpha$ , 5 $\alpha$ -THP in the hippocampus. This animal study is in agreement with previous research showing that estradiol is capable of inducing an increase in 3 $\alpha$ , 5 $\alpha$ -THP.<sup>27</sup>

In human studies, a positive correlation has been found between seizure susceptibility and the estrogen/progesterone ratio, with a peak in the premenstrual and preovulatory periods and a decline during the midluteal phase. Logothetis et al<sup>28</sup> have demonstrated that intravenous infusions of estrogen were associated with rapid interictal epileptiform activity in women with epilepsy, and that seizures were exacerbated when estrogen was given premenstrually. Therefore, it is hypothesized that estrogens may facilitate some forms of catamenial seizures observed during these phases. Logothetis et al<sup>28</sup> used conjugated equine estrogen containing alpha-estradiol, which is unnatural for humans, and most likely in excessive concentrations, as recent studies trying to replicate these findings using Premarin® in women with epilepsy did not find any exacerbation of seizures; this finding indicates that unnaturally high doses of estradiol may have deleterious effect.

The periovulatory catamenial exacerbation has been attributed to the midcycle surge of estrogen that is relatively unopposed by progesterone until early luteal phase.<sup>28</sup> An increase in the ratio of estrogen/progesterone levels during the perimenstrual period might at least partly contribute to the development of perimenstrual seizure exacerbation.<sup>11</sup>

Estradiol levels in women with catamenial epilepsy are lower in perimenstrual phase (~35 pg/mL) than the midluteal (~104 pg/mL) and follicular phases (~151 pg/mL). El-Khayat et al<sup>10</sup> found that in the perimenstrual phase, progesterone levels were lower and the estrogen/progesterone ratio was higher, in women with catamenial epilepsy. They also reported that in many patients with catamenial epilepsy, a marked increase in spike and wave discharges are observed during menstruation.<sup>10</sup> It seems too, that estradiol may play a prominent role in anovulatory cycles.<sup>29</sup> However, the exact relationship between circulating estrogens and the perimenstrual or anovulatory catamenial seizures remains unclear.

In contrast, there are several studies of chronic estrogen administration in females that show either anticonvulsant or no effect of estrogen on seizures.<sup>30-32</sup> In low doses, estradiol can produce neuroprotective effects.<sup>33</sup> The estrogen-induced neuroprotection was first demonstrated by Veliskova et al,<sup>31</sup> in status epilepticus models. The neuroprotective activity of estrogens was then confirmed by several subsequent studies.<sup>30,32,34</sup> It has been suggested that estradiol may prevent seizure-induced damage by modulating the hippocampal expression of glutamic acid decarboxylase (the principal enzyme for the synthesis of GABA),<sup>35,36</sup> and the modulation of neuropeptide Y expression.<sup>37</sup>

## Effects of progesterone

Animal and humans studies<sup>38,39</sup> clearly indicate that catamenial seizures are associated with a rapid decline in progesterone immediately before, during, and after menstruation.

In animal models, progesterone has been found to reduce neuronal firing and decrease spontaneous and induced epileptiform discharges.<sup>1,40,41</sup>

In clinical studies, progesterone has been found to reduce seizures.<sup>42,43</sup> Seizures decrease in the mid-luteal phase when serum progesterone levels are high, and increase premenstrually when there is a fall in progesterone levels and serum progesterone/estrogen ratio.<sup>16,44</sup> Changes in progesterone levels have been directly correlated with catamenial seizures.<sup>10</sup>

A recent study used transcranial magnetic stimulation to investigate the changes in cortical excitability during anovulatory and ovulatory cycles: the transcranial magnetic stimulation results obtained in women without neurological diseases could not confirm an inhibitory effect of progesterone on cortical excitability, as suggested by studies performed on rats.<sup>45,46</sup> Comparison of anovulatory with ovulatory cycles showed inhibition was greater in anovulatory cycles during the luteal phase despite the higher progesterone levels in ovulatory women. The rise in progesterone levels during the luteal phase of the ovulatory cycles and the progesterone withdrawal during menstruation did not induce significant changes in any of the transcranial magnetic stimulation parameters. Furthermore, there was no correlation between progesterone levels and intracortical inhibition.

Physiological actions of progesterone are mediated by progesterone receptors (PR), a member of the nuclear receptor superfamily of transcription factors. However, there is strong evidence that the antiseizure effects of progesterone are not related to interactions with classical PR; in fact, the antiseizure activity of progesterone was undiminished in PR knockout mice,<sup>1</sup> which are generated by a null mutation of the PR gene. Furthermore, some experimental studies,<sup>47,48</sup> have supported the concept that 5 $\alpha$ -reduced metabolites of progesterone, particularly allopregnanolone, are responsible for the seizure protection conferred by the parent hormone. Thus, the role of the PR in seizure susceptibility has not been fully explained. To date, a rapid effect of progesterone has been reported in the hippocampus slice excitability, that was blocked by the PR antagonist RU486.<sup>49</sup> In the hippocampus of adult rat, progesterone has opposite effects from estradiol. It causes a transient increase in dendritic spines over the first 6 hours of exposure, followed by a decrease in the number of CA1 dendritic spines and excitatory synapses. Progesterone also antagonizes estrogen actions, lowering estrogen receptor number.<sup>50</sup>

## Neurosteroids

Neurosteroids would be effective in modulating the function of GABA-A receptors:<sup>51</sup> in particular, allopregnanolone and pregnanolone have a positive effect on modulators of GABA-A receptors.<sup>51</sup> Accordingly, perimenstrual seizures may be caused by withdrawal of the antiseizure effects of neurosteroids.<sup>5</sup> Neurosteroids regulate GABA-A receptor plasticity,<sup>5,53</sup> and it is likely that they can have a role in ovarian cycle-related control of GABA-A receptor composition.<sup>5</sup> A further action of neurosteroids withdrawal is an evident increase in expression of the GABA-A receptor  $\alpha 4$ -subunit in the hippocampus,<sup>54</sup> with a consequent decrease in total GABA-gated current, an increase in seizure susceptibility, and changes in resistance to several classes of antiepileptic drugs.<sup>55</sup> These findings support the central role of  $\alpha 4$ -subunit changes, in neurosteroid withdrawal-linked catamenial epilepsy.

The basic molecular mechanism of the  $\alpha 4$ -subunit expression still remains to be determined. The relatively newly found early growth response factor-3 (Egr3) has been found to exhibit an important role in the regulation of  $\alpha 4$ -subunit expression in epilepsy models.<sup>56</sup> There are consistent findings that Egr3 levels in the hippocampus increase after recurrent seizures,<sup>56</sup> and after neurosteroid withdrawal.<sup>57</sup>

## Menopause and changes in seizures pattern

The marked hormonal changes that occur in the menopausal transition seem to have an effect on seizure susceptibility. Women with catamenial epilepsy may experience an increase in seizure frequency in perimenopause and a decrease after menopause, which is consistent with the high estrogen levels in perimenopause, and low estrogen levels in postmenopause.<sup>58</sup>

In experimental studies on ovariectomized animals where hormonal changes are abrupt, in contrast to the gradual hormonal changes found in the menopausal transition, the concerted lack of estradiol and progesterone may facilitate the seizure susceptibility. In fact, both estradiol and progesterone affect the GABA function; therefore, the simultaneous decrease of estrogen and progesterone may lead to a decrease in GABAergic inhibition, facilitating seizures.<sup>59</sup>

However, in human studies of other types of epilepsy, data regarding seizure frequency and severity during the premenopausal or postmenopausal period, are conflicting; in fact, some studies have shown that the frequency and severity of seizures in premenopausal women are similar to those in perimenopausal and menopausal women;<sup>60,61</sup> Abbasi et al

reported that about 40% of women with epilepsy had a worsening of their seizures after the menopause, some women had new onset of seizures, while only 18% had a better seizure control after the menopause.<sup>61</sup>

Interestingly, the standard hormone replacement therapy (which includes estrogen and a progestin) can be postulated to have an effect on seizures in postmenopausal women with epilepsy that is more evident than that of oral contraceptives in cycling women with epilepsy, because reproductive hormone levels during menopause are low and unchanging. The brain hormonal milieu in which exogenous hormones are introduced is markedly different in menopause from that in menstruating women.<sup>62</sup>

Finally, postmenopausal women with epilepsy deserve a special attention about the choice of the antiepileptic drugs: osteoporosis and fractures may increase due to hypogonadism in menopause and CYP P450-inducing antiepileptic drugs, such as phenobarbital, primidone, phenytoin, carbamazepine, oxcarbazepine and valproic acid, which have been implicated in promoting accelerated vitamin D metabolism, and bone loss.<sup>63</sup>

## Diagnosis

The diagnosis of catamenial epilepsy is established by careful assessment of menstrual and seizure diaries and characterization of cycle type and duration.

Some women with epilepsy appear to be at increased risk of ovulatory dysfunction. In a recent study, anovulatory cycles were found to be significantly more common in women with idiopathic generalized epilepsy (27%) than in those with focal epilepsy (14%), or in controls (11%).<sup>64</sup> Idiopathic generalized epilepsy, and the current use of valproic acid or use of valproic acid within 3 years, were predictors of ovulatory failure. However, in another investigation of 100 women with focal epilepsy, 39 had anovulatory cycles.<sup>65</sup> Some women have both ovulatory and anovulatory cycles requiring analysis of multiple cycles; in this group, seizure frequency appears to be greater during anovulatory cycles.<sup>11</sup>

## Treatment

Actually, there is no specific drug treatment for catamenial epilepsy, which is often refractory to many therapies.<sup>1</sup>

A variety of therapies for catamenial epilepsy have been proposed, including nonhormonal (acetazolamide, cyclical use of benzodiazepines, or conventional antiepileptic drugs), and hormonal therapies. However, evidence for the effectiveness of these treatments is not well established. Large

multicenter trials are needed to identify the most effective treatment for women with catamenial epilepsy.

## Hormonal therapy

Because progesterone has mainly been shown to have anticonvulsant effects, and because women with catamenial epilepsy under study often had inadequate luteal-phase or anovulatory cycles, it can be hypothesized that progesterone, progesterone metabolites, or estrogen antagonists may be used in conjunction with current antiepileptic medications, to treat these patients.

Natural progesterone, is a treatment option for patients with catamenial epilepsy and impaired luteal phase cycles. It is usually given in cyclic form during the luteal phase, taken orally at a dose of 100–200 mg, twice a day or three times a day. In fact, progesterone is poorly absorbed orally and has a short half-life, so that it must be administered multiple times per day. Over a 3-month period, 72% of the women reported a decrease in seizure frequency and the average daily frequency decreased by 55%.<sup>66</sup> Medroxyprogesterone acetate, a synthetic drug, can also reduce seizure frequency.<sup>67</sup>

Systemic oral contraceptive pills have not been found to decrease seizure frequency. Even though estrogen is a proconvulsant, combined oral contraceptives have not been associated with an increase in seizures. They may be used in women with epilepsy also to prevent unwanted pregnancies.

Gonadotropin releasing hormone analog, was studied in women with refractory perimenstrual seizures. The action mechanism of gonadotropin releasing hormone analog is the decreased luteinizing hormone and estrogen production with consequent amenorrhea. In one study, this was given intramuscularly in a controlled-release depot preparation every 28 days.<sup>68</sup> Generally, there was a significant reduction in the frequency of seizures, although Herzog et al found that women experienced an exacerbation of their seizures during the first 3 weeks of therapy, because a slight increase in ovarian estradiol production prior to inhibition.

Clomiphene is an ovulatory stimulant that is used to treat infertility in women with oligoanovulation or anovulation. Herzog<sup>69</sup> found that in 10 of 12 women with refractory, complex, partial epilepsy and menstrual disorders, the use of clomiphene decreased seizures by 50%.

Ganaxolone, a synthetic analog of allopregnanolone, is able to modulate most GABA-A receptors and is under investigation for the treatment of epilepsy. Laxer et al<sup>70</sup> completed a multicenter, double-blind, randomized, placebo-controlled, monotherapy clinical trial that evaluated the safety, tolerability, and antiepileptic activity of ganaxolone.

The study population consisted of 52 inpatients with medically-refractory, complex, partial seizures. Each patient was studied for up to 8 days, with patients receiving placebo or ganaxolone. The primary measure of antiepileptic activity was the duration of treatment prior to withdrawal from the study. Patients were withdrawn from the study at the occurrence of one of the following: four seizures of any type (with the exception of simple, partial seizures); three generalized tonic-clonic seizures; or status epilepticus. Fifty percent of the ganaxolone-treated patients completed the entire 8-day study, in comparison with 25% of the placebo-treated individuals. Tolerability of ganaxolone was similar to that of placebo. Ganaxolone may provide an effective approach for catamenial epilepsy therapy that is reliable, and that does not expose patients to the risk of hormonal side effects. New oral formulations of ganaxolone are going to be developed with enhanced bioavailability and more consistent absorption.<sup>71</sup>

## Non hormonal therapy

Acetazolamide, a carbonic anhydrase inhibitor, may be effectively used to treat catamenial seizures. This was demonstrated in a recent retrospective report on 20 women with temporal lobe, extra temporal, generalized and unclassified epilepsy, in which 30%–40% of the patients reported improvement in the frequency and severity of perimenstrual seizure exacerbations while taking acetazolamide.<sup>72</sup> Its mechanism of action is not well understood. It is clear, however, that tolerance develops, which results in diminishing efficacy over time. Therefore, this drug can only be administered on an intermittent basis, which is appropriate for catamenial epilepsy but not for ordinary seizure prophylaxis.

Synaptic GABA-A receptor-mediated inhibition can also be enhanced with benzodiazepines. Benzodiazepines are of limited utility in seizure prophylaxis however, they could theoretically be used on an intermittent basis for the treatment of catamenial seizures. In fact, 1,5-benzodiazepine clobazam, administered intermittently, has been used to treat catamenial seizure exacerbations over long periods of time with good results.<sup>73</sup>

## Disclosure

The authors report no conflicts of interest in this work.

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