CATAMENIAL EPILEPSY: FASCINATING INCIDENT IN EPILEPTOLOGY

Amruth Raj Veeduluri, Siddartha Kaskurthy and Vijay Krishna Nidadavolu

Department of Pharmacy Practice, Krupanidhi College of Pharmacy, 12/1, Chikkabellandur, Carmelaram Post, Varthurhobli, Bangalore-560035.

ABSTRACT
Catamenial epilepsy may be afflicted by Women. It is defined as changes in seizures severity during exacting phases of the menstrual cycle. Physiological endocrine secretion during the menstrual cycle influences the episode of seizures. Alterations in serum estradiol/progesterone ratio during a normal reproductive cycle convey increased or decreased risk of seizure occurrence. One-third to one half of women with epilepsy experience catamenial seizure. Awareness of the effects of sex hormones on epilepsy may open novel therapeutic approaches for women with catamenial seizures pattern. The aim of this article is to report the effects of sex hormones on epilepsy and to describe treatment approaches for catamenial epilepsy. The augment in seizure incidence during specific phase of menstrual cycle of the female, is greatly apprehensive of a diagnosis of Catamenial epilepsy. 33% of females with refractory seizures in their reproductive age group have this principal condition. Fluctuations in sex hormones can augment liability to seizures in many women. The low progesterone to estrogen ratio is a usually observed biochemical finding during these times. Large multicenter trials are desirable to recognize the most valuable treatment for women with catamenial epilepsy.

KEY WORDS: Catamenial epilepsy, Epileptology, Menstrual cycle, Seizure occurrences, Sex hormones.

INTRODUCTION
Catamenial Epilepsy is a fascinating incident in Epileptology. Women with epilepsy may have patterns of seizure related with changes in estrogen and progesterone levels. In
catamenial epilepsy, seizures have a tendency to cluster in relation to the menstrual cycle and causes greater increase in seizure frequency during a particular phase of the menstrual cycle.\[1-4\] It can affect from 10% to 70% of fertile women with epilepsy. Diagnosis of catamenial epilepsy constitutes the doubling of the baseline frequency of seizures, irrespective of type of seizure implicated, its localization or the epilepsy syndrome with a pattern of clustering, allied to patient’s menstrual cycle.\[6-11\]

**Correlation between epilepsy and the menstrual cycle**

It is assumed to occur secondarily to the neuroactive properties of endogenous steroid hormones and the natural cyclic discrepancy in their serum levels during the menstrual cycle. Herzog et al. illustrious three patterns of catamenial seizure exacerbation, concerning to the privileged seizure occurrence during the particular phases of the menstrual cycle:

- Perimenstrual (C1: Days -3 to 3)
- Periovulatory (C2: Days 10 to -13) in normal cycles, and
- Luteal (C3: Days 10 to 3) in scarce luteal phase cycles.\[12\]

Seizure occurrence (clustering of seizures) shows a statistically considerable positive association with serum estradiol/progesterone ratio in ovulatory cycles. This ratio is uppermost during the days preceding to ovulation and menstruation and is lowest during the early and mid-luteal phase. The premenstrual exacerbation of seizures has been endorsed to the quick removal of the anti-seizure effects of progesterone.\[13-15\]

Anovulatory cycles can arise even in women with regular menstrual cycles, even though the figure of anovulatory cycles increases with cycle length. Around 10% of menstrual cycles in healthy women are anovulatory, while 35% are anovulatory in women with temporal lobe epilepsy. Luteal phase of anovulatory cycle in women is characterized by little levels of progesterone, seizure frequency increases in the premenstrual phase for the reason that the mid cycle surge in estrogen still occurs, lacking a considerable augment in progesterone levels. Therefore, for up to 4 months a year, it is likely that woman may experience this third, nonspecific seizure pattern, which obscures detection of catamenial epilepsy. Quigg et al reported that youth increases seizure episode across the 28-day cycle.\[16-19\]

**Pathophysiology of catamenial epilepsy**

Estrogen and progesterone have significant effects on neuronal development through their ability to control synthesis, release, and transport of neurotransmitters.\[20-21\]
Estrogens have pro-convulsant and epileptogenic properties in animals and humans. There are two estrogen receptors, ERα and ERβ, through which estrogens establish their biological effects. The likely mechanism is that estradiol causes a down-regulation of glutamic acid decarboxylase enzyme. Logothetis et al have confirmed that seizures were exacerbated when estrogen was given pre-menstrually. As a result, estrogens may ease some forms of catamenial seizures observed during these phases. El-Khayat et al establish that in the perimenstrual phase of women with catamenial epilepsy, progesterone levels were lower and the estrogen/progesterone ratio was higher. The estradiol may play an outstanding role in anovulatory cycles. Conversely, the accurate correlation between circulating estrogens and the anovulatory catamenial seizures remains ambiguous. Estradiol can produce neuroprotective effects. The estrogen-induced neuroprotection was demonstrated first by Veliskova et al in status epilepticus models and then established by several succeeding studies. It has been recommended that estradiol may avert seizure-induced damage by modulating the hippocampal expression of glutamic acid decarboxylase and neuropeptide Y expression.  

Progestosterone and epilepsy

Catamenial seizures are related with a quick turn down in progesterone instantly before, during, and after menstruation was evidently indicated by animal and human studies. Seizures reduce in the mid-luteal phase when serum progesterone levels are high, and increase premenstrually when there is a decrease in progesterone levels and serum progesterone/estrogen ratio. Alterations in progesterone levels have been openly associated with catamenial seizures. Physiological actions of progesterone are mediated by progesterone receptors (PR), a part of the nuclear receptor super-family of transcription factors. Some experimental studies have supported that 5α-reduced metabolites of progesterone (allopregnanolone), are accountable for the seizure protection conferred by the parent hormone. Progesterone antagonizes estrogen actions by lowering estrogen receptor number.  

Neurosteroids and epilepsy

Perimenstrual seizures may be caused by extraction of the antiseizure effects of neurosteroids. These control GABA-A receptor plasticity and it is probable that they can have a role in ovarian cycle-related control of GABA-A receptor composition. The recently found
early growth response factor-3 (Egr3) has been found to demonstrate an imperative role in the regulation of α4-subunit expression in epilepsy models.\cite{46-52}

Women with catamenial epilepsy may experience an increase in seizure regularity in perimenopause and diminish after menopause, which is steady with the high estrogen levels in perimenopause, and low estrogen levels in postmenopause. Mutually estradiol and progesterone affect the GABA function; as a result, the instantaneous reduce of estrogen and progesterone may direct to diminishin GABAergic inhibition, facilitating seizures. Abbasi et al reported that around 40% of women with epilepsy had an aggravation of their seizures after the menopause, several women had new onset of seizures, whereas just 18% had an improved seizure control after the menopause. Postmenopausal women with epilepsy justify an extraordinary concentration about the selection of the antiepileptic drugs.\cite{53-56}

**Diagnosis**

The diagnosis of catamenial epilepsy is reputable by cautious estimation of menstrual and seizure diaries and categorization of cycle type and duration.\cite{57}

**Management**

There is no exact drug treatment for catamenial epilepsy, which is often intractable to many therapies. For catamenial epilepsy, an array of therapies has been projected, include Non-hormonal therapy (acetazolamide, cyclical use of benzodiazepines, or conventional antiepileptic drugs) Hormonal therapies.\cite{58}

Facts for the effectiveness of these treatments are not well reputable still now.

**Non hormonal therapy**

Acetazolamide (carbonic anhydrase inhibitor) may be effectively used to treat catamenial seizures. Its mechanism of action is not well implicit. This drug can only be administered on an alternating basis, which is suitable for catamenial due to diminishing efficacy over time. Benzodiazepines are of restricted utility in seizure prophylaxis. Clobazam administered sporadically, has been used to treat catamenial seizure exacerbations over long periods of time with superior results.\cite{59-60}

**Hormonal therapy**

Progesterone, progesterone metabolites, or estrogen antagonists may be used in combination with existing antiepileptic medications. Progestogentreatment in two forms Cyclic
progesterone therapy- supplements progesterone during the luteal phase and withdraws it gradually premenstrually.

Suppressive therapy is to restrain the menstrual cycle which is usually proficient using injectable progestins or GnRH analogs.

Natural progesterone is a treatment choice for patients with catamenial epilepsy and impaired luteal phase cycles. It is generally 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. 72% of the women reported a reduction in seizure frequency over a 3-month period.

Medroxyprogesterone acetate, a synthetic drug, can also lessen seizure frequency.

Gonadotropin releasing hormone analog acts by decreased luteinizing hormone and estrogen production with consequential amenorrhea.

Clomiphene (ovulatory stimulant) is used to treat infertility in women with oligoanovulation or anovulation.

Ganaxolone (synthetic analog of allopregnanolone) is capable to modulate most GABA-A receptors and is under investigation for the management of epilepsy. [61-66]

CONCLUSION
The augment in seizure incidence during specific phase of menstrual cycle of the female, is greatly apprehensive of a diagnosis of Catamenial epilepsy. 33% of females with refractory seizures in their reproductive age group have this principal condition. Fluctuations in sex hormones can augment liability to seizures in many women. The low progesterone to estrogen ratio is a usually observed biochemical finding during these times. Large multicenter trials are desirable to recognize the most valuable treatment for women with catamenial epilepsy.

REFERENCES


