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Catamenial epilepsy

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Abstract
Epilepsy is a commonly encountered neurological condition characterised by recurrent episodes of unprovoked seizures. Epilepsy acts as a broad terminology that includes any abnormal mechanism in brain which cause an electrical short circuit or electrical storm that manifests as seizure1. Epilepsy affects both adults and children. Epileptic seizures can occur with wide variation in presentation and to provide effective appropriate treatment, systematic precise classification of epilepsy is mandatory. Seizures are mainly divided into partial and generalized seizures, but some are unclassified. The common definition of catamenial epilepsy is, "the seizure clusters occurring around menstrual cycle or an increased seizure frequency during certain phases of menstrual cycle". Some female sex hormones and certain steroid gonadal hormones have neuroactive properties that can trigger seizures. Though there are many subtypes in catamenial epilepsy, neurosteroids have been found to influence the seizure clusters in women who have normal 28 day menstrual cycles who suffer during the perimenstrual period. It is thought that progesterone derived neurosteroids withdrawal causes enhanced stimulation or excitability of cerebral cortex which predispose to seizures. Varied concentrations of anticonvulsants during the different phases of menstrual cycle also because increased seizure susceptibility.

Keywords: Brain, catamenial, epilepsy, menstrual cycle, seizures

Introduction
Catamenial epilepsy has been observed in 10%-70% of epileptic women with recurrent exacerbations. There is a wide percentage of prevalence of catamenial epilepsy as reported by many studies due to self-observed reports, seizure-menstrual cycle diaries of women with pharmaco-resistant and refractory epilepsy. But this entity has gained much attention and awareness though there is no lucid or globally accepted criteria for diagnosing catamenial epilepsy. Catamenial Epilepsy is defined as cyclical increase in seizure frequency during or around the time of menstrual periods [1]. Duncan *et al*. (1993) defined, "Catamenial epilepsy as having 75% of seizures during a 10 day period of menstrual cycle beginning 4 days before menstruation". Newmark and Penry (1980) defined, " perimenstrual catamenial epilepsy as epileptic seizures occurring in women of fertile age exclusively or significantly more often during a 7-day period of the menstrual cycle, beginning 3 days before menstruation and ending 4 days after its onset". Herzog *et al*. (1997) defined, "Catamenial epilepsy as a greater than average seizure frequency during perimenstrual or periovulatory periods in normal ovulatory cycles and during the luteal phase in anovulatory cycles". All the above definitions are arbitrary, not definite, variable and less uniformity in definition. According to Reddy (2007), "a two-fold or greater increase in seizure frequency during a particular phase of the menstrual cycle may be defined as catamenial epilepsy"15. This explanation can be used as a standard criterion in studies to analyse the pathophysiology and treatment of catamenial epilepsy. By using this criteria, about one third of women with intractable epilepsy would be classified under the category of catamenial epilepsy [2]. By adopting a standard nomenclature, greater uniformity may exist 12 in studying the pathogenesis and treatment of catamenial seizure exacerbation. Herzog *et al*., in his study classified catamenial epilepsy into three patterns:

1. Perimenstrual (C1): Days -3 to 3
2. Periovulatory (C2): Days 10 to -14
3. Luteal (C3): Days 10 to day 3

In the above classification, Day 1 denotes the first day of menstrual flow and ovulation is presumed to occur 14 days prior to onset of the next cycle (-14). The above mentioned patterns were demonstrated by charting the menses and seizure occurrence and estimating the mid-luteal serum progesterone level to differentiate between normal and inadequate luteal phase cycles.

Pathophysiology [3-5]

Catamenial epilepsy is believed to occur due to rhythmic and cyclic variations of the gonadal hormone levels and the drug metabolism. The epileptic women with catamenial exacerbation have their seizure clusters at or shortly after menarche. They show excessive EEG activity during the menstrual cycle. Oestrogen increases the seizure propensity and Progesterone decreases it. Progesterone and estrogen influences the development and plasticity of neurons in diffuse cerebral and brainstem areas by regulating the synthesis, release and transport of certain neurotransmitters like GABA, glutamate and by altering the brain excitability18. Particularly during two specific times of menstrual cycle, the seizure cluster frequency increases, during the days prior to menses when progesterone level is low and then before ovulation when the oestrogen level is high. The frequency of seizures also increases when the cycles are anovulatory during which time the progesterone levels are again low. In women with normal ovulatory cycles, the increased values of estradiol and progesterone ratio prior to the onset or during menstruation may be the reason behind the seizures. When the progesterone action no longer exists, same as that when benzodiazepines are stopped suddenly in a patient with epilepsy, the seizure exacerbation might occur in the premenstrual period. During the time before ovulation, the levels of oestradiol increase and this 18 might lead on to seizure exacerbation during the periovulatory period. The luteal phase is free of seizure or rarely the seizures occur as the progesterone is at its peak compare to oestrogen. During anovulatory cycles, the luteal phase has low levels of progesterone and so the seizure frequency hikes up during the premenstrual period as the oestrogen level increases during the middle of menstrual cycle but without increase in progesterone level. In some healthy women with normal menstrual cycle, 8-10% has anovulatory cycles. Several studies suggest the presence of different types of cyclic rhythmic pattern of seizures in women. So, the types of treatment option for catamenial epilepsy also differ and depend upon the exact phase of the menstrual cycle the seizure clusters occur.

Diagnosis [6-7]

Catamenial epilepsy may be diagnosed by the evaluation of menstrual cycle and the seizure reporting diaries, by characterising the cycle type and duration. Few epileptic women have excessive risk of dysfunction of ovaries. In a recent study 25% of epileptic women with generalized seizures were found to have anovulatory cycles compared to women with focal seizures. So the generalized seizures may be considered as predictor for ovarian dysfuction which could cause failure of ovulation

The best way to assess if there is worsening of seizures during certain phases of menstrual cycle is to have the patient maintain a note of the seizure clusters in relation to her menstrual cycle. Taking the first day of menstrual bleeding as the first day of the menstrual cycle, it is divided into four phases:

1. Menstrual phase: Days -3 to 3
2. Follicular phase: Days 4 to 9
3. Ovulatory phase: Days 10 to 16
4. Luteal phase: Days 17 to -3

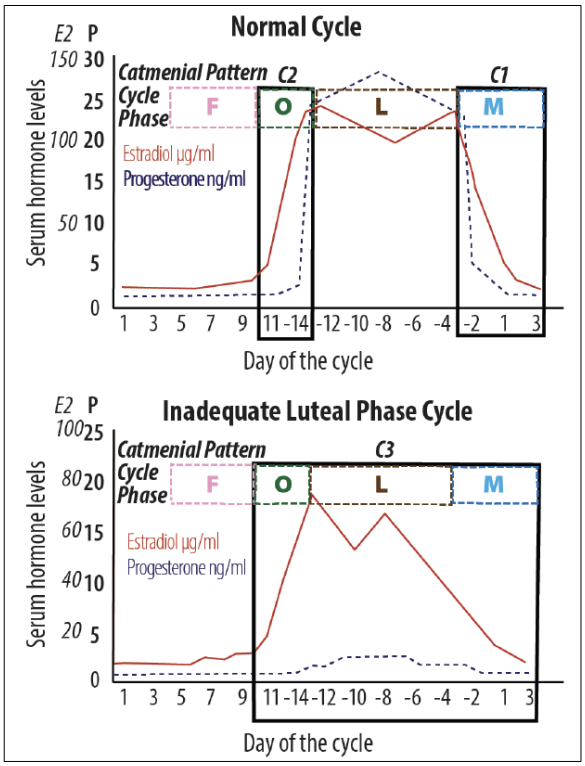

Fig 1: Patterns of catamenial epilepsy

Treatment [8-12]

The management of catamenial epilepsy may be done by adjusting the medications the patient is already taking, non-hormonal and hormonal 29 therapy. If the antiepileptic drug levels were proved to be low during the seizure clusters or during particular phases of menstrual cycle, increasing the AED dose or adding another AED often a benzodiazepine around that particular time would be helpful in decreasing the seizure frequency. In the past years, many empirical measures of adjusting the pre-existing AED dose or adding another AED mostly a benzodiazepine had been tried in management of the catamenial exacerbation. But these studies were not randomised or blinded or controlled trials. Aggressive measures like hysterectomy or oophorectomy, hormonal manipulation by giving hormone containing contraceptive pills, naturally occurring progesterone and clomiphene have been tried. Other treatment strategies include adding acetazolamide to the AED during the perimenstural period. Actually there is no particular drug therapy for catamenial epilepsy proven till date as this condition is refractory to many therapies. Among the variety of therapies proposed, adding acetazolamide, benzodiazepines or conventional anticonvulsant drugs with dose adjustment during the particular phases and hormonal therapies are useful. However, the proof for the efficacy of these treatment modalities is still not very clearly established. Multicentre trials may be required to assess the effective treatment for these women with catamenial exacerbation.

Conclusion

A wide population of women with epilepsy is treated with multiple anticonvulsants and are considered refractory to treatment. The under recognition and lack of awareness of catamenial epilepsy could be one of the reasons behind the polytherapy of anticonvulsants in many such women, especially in our country. There are very few studies analysing the prevalence of catamenial epilepsy in our country. Among the women with pharmacoresistant epilepsy, about one fifth of women according to our study fall under the category of catamenial epilepsy where the appropriate treatment strategy would reduce the burden in the lives of these epileptic women.

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