

## INFLUENCE OF STEROID HORMONES IN WOMEN WITH MILD CATAMENIAL EPILEPSY

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**Background:** In view of considerable differences of opinion regarding the reproductive steroid hormonal pathogenesis in catamenial epilepsy, hormonal analysis of estrogen and progesterone in catamenial epileptics for a precise correlation is of significant importance. **Methods:** Clinical, neurological and physiological assessments, and radioimmunoassay of plasma estradiol-17 $\beta$  and progesterone a day prior to the onset of menstruation were carried out in noncatamenial and mild catamenial epileptics having multiple frequency tonic-clonic (primary and secondary generalized) seizures. **Results:** Highly significant rise ( $p > 0.0001$ ) of estradiol-17 $\beta$  was obtained for catamenial epileptics compared to normal subjects as well as noncatamenial epileptics ( $p > 0.02$ ). However, nonsignificant fluctuations of progesterone were found for both catamenial and noncatamenial epileptics against normal subjects as well as catamenial versus noncatamenial epileptics. **Conclusions:** The present report suggests that estradiol have a precise role in the mild premenstrual exacerbation of seizures. However, no significant change in progesterone levels might have been due to mild exacerbation of seizures in these patients. Furthermore, we suggest the importance of how we collect and categorize the data and which pathophysiologic process/clinicobiological mechanism is involved in patients with catamenial epilepsy. Contradictory results in literature may be related to differential levels of excitation/inhibition equilibrium during various cycle phases. More precise studies including the determination of the blood levels of antiepileptic drugs, however, are required.

**Key Words:** Estradiol, progesterone, mild catamenial epilepsy

### INTRODUCTION

Catamenial epilepsy is considered as a menstrual cycle-related seizure disorder and is characterized by an increase in seizures during particular phases of the menstrual cycle<sup>1</sup>. Immediately or several days before menstruation, however, is considered as the most prevalent pattern<sup>2-4</sup>.

Role of estrogen and/ or progesterone in relation to catamenial epilepsy has been studied by several investigators<sup>10-12</sup>. However, there have been considerable differences of opinion regarding the hormonal pathogenesis of the catamenial exacerbation of epileptic seizures<sup>3,5,7</sup>. Thus, hormonal analysis of estrogen and progesterone in catamenial epileptics for a precise correlation is of significant importance.

Although a convulsive effect of estrogen have been shown<sup>13</sup>, one study, however, involving estimation of ovarian hormone levels during the menstrual cycle of patients with epilepsy<sup>6</sup> have not confirmed the earlier suggestion by Logothetis et al.<sup>13</sup> that high levels of estrogen are responsible for the catamenial exacerbation of seizures. Pennell et al.<sup>14</sup> also did not find consistent correlation between average daily seizure frequency and hormonal levels in one woman with perimenstrual seizures. On the other hand, the effect of intravenous progesterone infusions on epileptic discharge frequency<sup>15</sup> indicated

a significant decrease in spike frequency in few of the patients studied.

These studies stress the importance of investigating the precise role of estradiol and progesterone in women with catamenial and non-catamenial epilepsy. Therefore, the main objective of the present study is to test the hypothesis that estrogen and/ or progesterone play important role in the pathogenesis of catamenial epilepsy. Elucidation of this information may help to have particular social and medical measures to reduce the incidence of mild and severe forms of catamenial epilepsy.

### MATERIAL AND METHODS

Non-catamenial epileptics (NCEp; n: 236) and catamenial epileptics (CEp; n: 164) having tonic-clonic (primary and secondary generalized) seizures were observed mainly at the Department of Neurology (formerly Department of Neuropsychiatry), Jinnah Postgraduate Medical Centre (JPMC), Karachi during 1984 to 1988 and 1990 to 2001. Normal young women (N; n: 105) served as control subjects. Body weight (Lbs.) in normal subjects, non-catamenial epileptics and catamenial epileptics was in the range of 71-138, 72-131 and 62-125 respectively. Radioimmunoassay (RIA) determination for steroid hormones were carried out at a WHO collaborative "National

Research Institute of Fertility control" (NRIFC), Karachi. Detailed methods of the clinical, physiological, neurological and hormonal evaluations are mentioned elsewhere<sup>3,8</sup>. In the present report, we applied the definition of catamenial epilepsy and catamenial epileptic seizures as described by Gastaut<sup>16</sup> in the Dictionary of Epilepsy. For statistical evaluation of the present part of data, arithmetic mean, standard error of the mean, Student's t test, z test and correlation coefficient 'r' were performed and significance values (p) were determined.

Any past history of CNS insult; family history of epilepsy; CNS disorders; accident and also consanguinity were recorded. The patient was asked to describe pre-ictal, ictal, and post-ictal sensations. The cards also had information on seizure frequency; duration of each attack; time of seizure occurrence; any aura; and whether seizures affected one or both sides of the body. Specific questions were asked whether any stimuli or precipitants e.g. loss of sleep, fever, tiredness, noise, emotional disturbances, photosensitivity etc. provoked a seizure. Also whether it was clonic, tonic or tonic-clonic; partial or complete loss of consciousness during the attack. Records were obtained for incontinence, tongue biting and injury, age of onset of the disorder, duration of illness, previous and present record of medication and efficacy of prescribed drugs (mainly carbamazepine, phenytoin, phenobarbitone, primidone, ethosuximide, valproate etc). The required dosages of combined drug polypharmacy were prescribed while relying on the drug blood levels already established. Nausea, vomiting, headache, tdds, paralysis and other postictal phenomena were noted; and clinical tests (EEG, radiological, biochemical) were performed. Complete neurological examination and differential diagnosis of epileptic seizures was considered and faints (syncope), sleep disorders, hysteria, other disorders resembling epilepsy like Meniere's disease, hyperventilation or breathing attacks, drop attacks, carotid sinus disorder, nervous ticks etc. were excluded. Initial data from Pakistan<sup>18</sup> and personal experience of dealing with epileptic women for few months lead to the decision to select and follow up non-catamenial and catamenial epileptics with only tonic-clonic (primary generalized and secondary generalized) seizures<sup>17</sup>. Various tests of these patients were performed.

The subjects having previous 4 menstrual cycles as regular (cycle length: 25-35 days) were included in the study. Duration of menstrual cycle

was considered from the first day of menstrual bleeding (included) to the first day of next bleeding (excluded). One day prior to the onset of menstruation was designated as day -1<sup>3</sup>. Record of menstruation duration and basal body temperature (BBT) was also obtained to analyze the cycle length and ovulatory nature of the cycle. Samples of blood were taken and plasma separated. Samples were stored at -20° C till needed for assay. The samples required for steroid assay were obtained from extraction of plasma with equal amount of diethylether (50: 50) following the method as recommended by WHO. The detailed RIA methods and preparation of standards for estrogen and progesterone are mentioned in a previous comprehensive report<sup>3</sup>.

## **RESULTS**

One day prior to the onset of menstruation (day -1) in normal subjects and women patients with noncatamenial and catamenial epilepsy was studied (Table I). Mean seizure occurrence (average 13 seizures) on day -1 in epileptics with seizures of multiple frequency patterns was significantly higher in catamenial compared to non-catamenial epileptics ( $p < 0.05$ ). Age of the patients and normal subjects did not vary significantly. No significant variations in menstruation duration were found. Comparison for cycle duration showed significant variation ( $p < 0.001$ ; Table I) for catamenial against noncatamenial epileptics only for those patients having cycle duration less than 28 days.

Estradiol values (mean  $\pm$  S.E.M) for normal subjects and women with noncatamenial and catamenial epilepsy are given in Table I. Highly significant rise ( $p > 0.0001$ ) was obtained for catamenial epileptics compared to normal subjects as well as noncatamenial epileptics ( $p > 0.02$ ). However, noncatamenial epileptics compared to normal subjects did not show significant variations. Correlation coefficient 'r' for seizures against plasma estradiol showed nonsignificant correlation ( $p > 0.05$ ) for both group of patients.

Mean  $\pm$  S.E.M values of progesterone for normal subjects and patients with noncatamenial and catamenial epilepsy are given in Table I. Analysis indicated nonsignificant fluctuations for both catamenial and noncatamenial epileptics against normal subjects as well as catamenial versus noncatamenial epileptics. The values of 'r' showed no definite relationship found for seizure occurrence against progesterone levels.

**Table-1: Steroid hormones and reproductive profile in patients with catamenial/ noncatamenial epilepsy.**

Parameters	Normal subjects (N) (n: 105)	Noncatamenial epileptics (NCEp) (n:236)	Catamenial epileptics (CEp) (n:164)	Significance (p)		
				NCEp vs N	CEp vs NCEp	CEp vs N
Menstruation duration (days)	4.78 ± 0.05	4.86 ± 0.04	4.95 ± 0.06	>0.05	>0.05	>0.05
Cycle duration (days)	28.63 ± 0.12	28.60 ± 0.07	28.50 ± 0.10	>0.05	<0.001	>0.05
Estradiol-17β (pmol/l)	222.48 ± 9.42 (76)	242.95 ± 5.84 (143)	264.89 ± 8.53 (92)	>0.05	>0.02	>0.0001
Progesterone (nmol/l)	14.29 ± 0.85 (76)	15.49 ± 0.55 (143)	13.69 ± 0.80 (92)	>0.05	>0.05	>0.05

Figures in parentheses denote total number of samples; the data of age, menstruation duration and cycle duration is of all subjects.

## DISCUSSION

In the present study, the pattern of estradiol and progesterone concentration is similar to that in normal subjects<sup>19</sup> and those with epilepsy<sup>7</sup>. Majority of the women studied by Backstrom<sup>5</sup> also shows a similar pattern. The results of the subjects with multiple seizure frequency pattern in the present investigation though resemble to other reports in respect to some aspects of the patients' categorization and neurological and hormonal evaluations<sup>6,7,8</sup>, it was restricted to the study of one day prior to the start of menstruation that helped comparing precise hormonal variations in catamenial and noncatamenial epileptics.

Significant variation of seizure occurrence ( $p < 0.05$ ) with corresponding estradiol variations ( $p > 0.02$ ) shows that a relationship exists between estradiol levels and seizures in catamenial epileptics and estradiol have a precise role in the premenstrual exacerbation of seizures. Furthermore, the comparison with normal subjects showing highly significant change in estradiol only in catamenial epileptics confirming our previous reports<sup>28</sup> clarified that possibly the prescribed treatment did not alter the plasma estradiol levels.

No significant change in progesterone levels seems to be due to a different dispersion pattern of seizures in these patients compared to our another group of patients with severe catamenial epilepsy<sup>8</sup>. Instead of seizures occurring mainly or exclusively during premenstruation, the present group of patients had seizures also during other cycle phases though quite less in number than during premenstruation. In view of this, the term mild catamenial or semi-catamenial may be used for those patients who have a mild exacerbation. This may suggest that the

pathophysiological processes/ mechanisms in these patients might have been different. This background may explain the difference in the positions taken by two eminent researchers where Laidlaw<sup>20</sup> was more in favor of progesterone hypothesis, and Logothetis<sup>13</sup> was more inclined to implicate estrogen.

The present study suggests that some specific alteration in neural and hypothalamo-hypophyseal-ovarian (H-H-O) complex may be the stimuli that result in changing hormone levels<sup>3,17</sup>. This view may also explain the significant variations found in estradiol for normals and non-catamenial and catamenial epileptics. The results of estrogen activation hypothesis<sup>13</sup> in this respect are in agreement with animal experimentation<sup>21</sup>. On the basis of our previous investigations<sup>3,8</sup> and present work, we suggest that it is probably not the variation of estrogen or progesterone or any other particular hormone/ factor causing all sub-types of catamenial epilepsy/ epilepsy during menstrual cycle. Rather it is how we gather and categorize the data and which pathophysiologic process/ clinicobiological mechanism is involved in certain group of patients with noncatamenial/ catamenial epilepsy. Further work is obviously required to interpret the controversial views in literature.

## CONCLUSIONS

Contradictory results for the role of gonadosteroids in literature may be related to differential levels of excitation/inhibition equilibrium during various cycle phases<sup>22</sup>. Although previous investigations which included determination of blood levels of the antiepileptic drugs did not find any significant variations in levels of antiepileptic drugs, more precise studies including the determination of the blood levels of antiepileptic drugs are required. This

may help understanding the precise role of reproductive steroid hormones in catamenial epilepsy.

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