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No effects of the gonadal hormones on photoparoxysmal EEG responses in idiopathic generalised epilepsy

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ABSTRACT

Purpose: It is accepted that the estrodiol hormone is proconvulsant and progesterone is anti-convulsant. In this study the effects of gonadal hormones on photoparoxysmal responses on EEG in idiopathic generalised epilepsy were researched.
Method: Twenty-two women with photosensitive idiopathic generalised epilepsy having regular menstrual cycles were recruited into the study. Patients presenting photoparoxysmal responses were selected from routine EEG recordings. Blood samples were taken on day 14 (E) and 25 (P) of the menstrual cycle to confirm E and P peaks. An EEG recording was performed for each patient on E and P days.
Result: No statistically significant differences were monitored with respect to frequency, duration of the photoparoxysmal responses on E and P peaks days ($p > 0.05$).
Comment: In this study no correlation could be demonstrated among menstrual cycle and photoparoxysmal responses.
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1. Introduction

Seizures do not occur randomly, rather they cluster around certain periods of menstrual cycle in female patients and this pattern is defined as catamenial epilepsy.[1] Heading from these observations many researches have inquired the effect of gonadal hormones on epileptic seizures. Consequently, it is indicated that the estrogen hormone acts as proconvulsant and progesterone as anti-convulsant.[2] But on experimental studies it is pointed out that especially the proconvulsant effects of estrodiol cannot be shown consistently in all studies.[3]

The most frequent reflex precipitant for epileptic seizures is the photic stimulation. Even if there is no clinical manifestation, some patients usually in idiopathic generalised epilepsy (IGE) group, exhibit paroxysmal photoconvulsive responses (PPRs) (spike and wave, multiple spike and wave activities) during intermittent photic stimulation (IPS).[4] Despite that catamenial epilepsy is often observed in focal epilepsies, it is known that menstrual period may trigger seizures in photosensitive and IGE patients, also.[4] In a study where the excitability of motor cortex is evaluated in a group of 6 patients with catamenial epilepsy including one IGE, it is observed that cortical silent periods shorten during menstruation and is explained with decreased GABAergic inhibiton.[5]

Another remarkable feature is that the photosensitivity is more often observed in women.[4] The contribution of gonadal hormones on this tendency is not known. To our knowledge, there is not any study in the literature regarding the role of menstrual cycle on PPRs. Thus, in this study the effect of menstrual cycle thus of the gonadal hormones on PPRs is evaluated.

Our statement is that if the estrogen is a proconvulsant hormone, it can have an increasing effect on PPRs or vice versa.

2. Method

Female patients presenting PPRs during routine EEG recordings in our EEG laboratory and who had regular menstrual cycle story (28 ± 1 days) were included in the study. Any degree of PPRs according to Waltz et al. criteria were allowed for inclusion to the study. Spontaneous discharges on baseline EEG were not used as a criteria for exclusion or inclusion. No catamenial pattern was reported in this sample. Progressive myoclonic epilepsies were excluded. There was no consideration with regards to time interval between baseline EEG and the first study EEG. Certain drugs and changes in drug regime at baseline EEG and during study period was not regarded as an exclusion criteria.

Blood samples were taken on day 14 (E) and 25 (± 1) (P) of the menstrual cycle to confirm E and P peaks (95–433 pg/ml interval was accepted to be sufficient for estrogen peak, 5.1–18.5 ng/ml interval for progesterone).[2,6,7]

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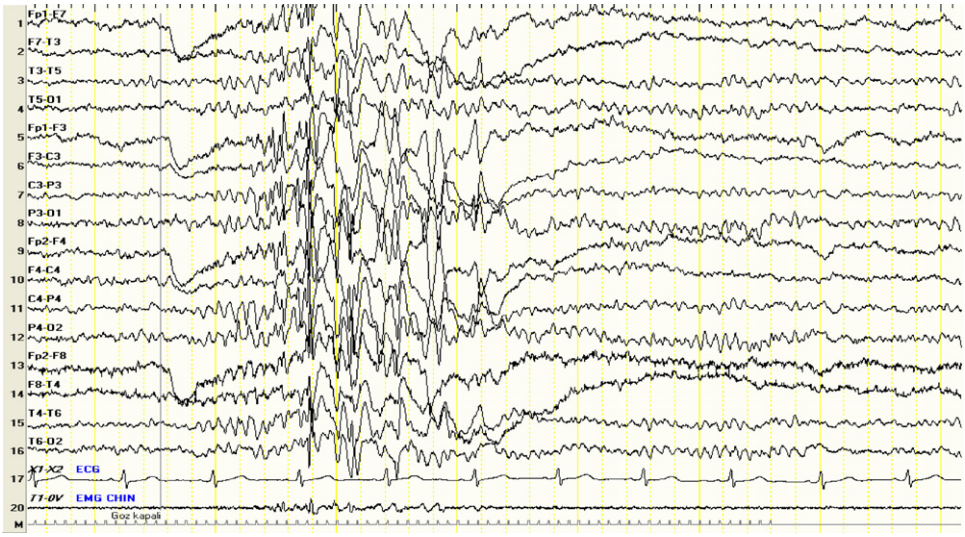


Fig. 1. A photoparoxysmal response of patient 20 during estrogen phase (HF: 70 Hz, TC: 0.3 sn, sensitivity 7 μV).

An EEG was recorded on days E and P. A 16 channels Nihon Kohden device and LS-901A photic stimulator was used for recordings. The stroboscope stimulating white light was rectangular. Electrodes were placed according to 10–20 electrode montage system. IPS protocol was designed as 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 50, 60 and then 60, 50, 33, 30, 27, 24, 21, 18, 15, 12, 9, 6, 3, 1. Each stimulus period was carried out 10 s, eyes open for the first 5 s and then with eyes shut(in between interval is 10 s). The source of the stimulus was held at 30 cm far to the nasion of patient. The intensity of stimulus was set as 0.64 J, and its luminance value was set as 4 lx. Stimulation was presented in a dim room light.[4,8–10] Patients attended the examination after a full night sleep and full. Antiepileptic drugs were not stopped. Changes in drugs and their dosage were allowed during the study period.

EEG recordings were evaluated by two independent neurologists (1st and 2nd authors). No consensus was composed in three patients and after evaluation by a third neurologist, a consensus was established (4th author).

Spike and wave, multiple spike and wave discharges spontaneously and also during IPS were evaluated. They were compared with respect to changes on days E and P. Parameters for comparison of photoparoxysmal responses were frequency of discharges, frequency bands at which they were monitored, duration of the PPRs, absence–presence of the discharge according to open–closed eyes state and continuation of discharge after the termination of the stimulus and presence of spontaneous discharges (Figs. 1 and 2). On the evaluation of photoparoxysmal responses, the classification of Waltz et al. was used and any degree of PPRs were included in comparisons.[11]

For statistical analysis NCSS (number cruncher statistical system) 2007&PASS 2008 Statistical Software (Utah, USA) program was used. For the comparison of quantitative data Wilcoxon sign test was used. Chi-square test and Mc Nemar tests are used on the comparison of qualitative data. Relevance was evaluated at $p < 0.05$ level.

3. Results

Twenty-two female patients were included in the study. The average age of patients was 24.73 ± 8.48 years. All of the cases were classified as having idiopathic generalised epilepsy (4 isolated generalised tonic clonic attacks, 4 absence syndromes, 1 photosensitive epilepsy, 13 juvenile myoclonic epilepsy). The average epilepsy duration was 9.8 years. Eighteen cases were receiving Na Valproate



Fig. 2. A grade I photoparoxysmal response of patient 4 during progesteron phase (HF: 70 Hz, TC: 0.3 sn, sensitivity 7 μV).

treatment (avarage 500 mg/day), one case valproate and topiramate treatment, one case carbamazepine treatment, and two patients did not receive treatment at the beginning of the study (during baseline EEG), valproate 500 mg/day was started during the study period. Eleven patients were in remission, 7 patients had seizure recurrence due to low dose, incompliance, utilization of carbamazepine. The response to treatment was insufficient in monotheraphy in two patients, lamotrigine was added-on in these patients as to be titrated.

PPRs were monitored in 16 of 22 patients on day E and in 14 of them on day P. In two patients PPRs were observed on day E only and in one patient on day P only. There were no statistical difference with respect to above parameters on PPRs on days E and P ($p < 0.05$) (Table 1). In a group of five patients no PPRs were observed on both days. The mean age of this group was 23.05 and there was no statistical difference between the ages of discharge positive group ($p = 0.204$) (mean age of PPRs positive patients: 21). The correlation of number and duration of PPRs as with regard to age revealed no significance (Table 2).

4. Discussion

In this study the effects of estrodiol and progesterone hormones on PPRs were reviewed in female patients and no statistical differences were found.

As the patients were in variable phases of cycle during baseline EEG, this EEG was not included in comparisons. It seems that an additional recording during the menses would be contributory.

In none of the cases, ovulation follow-up was performed with ultrasonography and serial hormone levels could not be monitored. Even if the estrogen, progesterone levels were in expected ranges, the defined interval was notably wide and it was not possible to make a comment on the existence of ovulatory cycles of the patients and whether being at full peak periods on days of EEG recordings.

Not all the patients exhibited PPRs on the study EEG recordings. Incompliance to treatment and seizure recurrences before baseline EEG and changes in drugs during study period may account to this discrepancy.

Two patterns were reported for ovulatory cycles in catamenial epilepsy.[2] Seizures increase around menses and during days coinciding ovulation under the influence of gonadal hormones. There are various ways how sex hormones affect seizures. Steroids act in the brain by direct membrane mediated effects and receptor mediated effects (short latency and long latency, respectively).[12] Estrodiol increases the glutamate response of neurons. Furthermore it is also effective on membrane excitability through binding to GABA-A receptor and by cytosolic neuronal estrogen receptor-mediated mechanisms. These receptors are particularly abundant in the temporo-limbic system, therefore explaining the higher frequency of catamenial seizures in temporal lobe epilepsies.[12] Long latency effects cause structural and functional changes at excitatory synapses.[13,14] Genomic effect of estrogen is through affecting mRNA, changes the synthesis speed of GABA, coding the GABA amino decarboxylase (GAD) enzyme and decreasing the synthesis of GABA receptor subunits (12, 14).

Progesterone increases the entrance of chloride ions inside the cell through GABAergic ways. Furthermore it is proposed that progesterone decreases excitatory glutamatergic effects in the temporal lobe. It also increases GABA synthesis and the number of GABA-A receptor subunits genomically.[2,12–15]

Frontorolandic and occipital cortex seem to be the most involved areas in generating PPRs.[16] There is ample evidence that PPRs is genetically determined.[16,17] GABAergic mechanisms may play an important role in the pathophysiology of photosensitivity, and that GABAergic agonists may suppress PPRs.[16] Animal models suggest that many other neurotransmitters have a role in the generation of photosensitivity in idiopathic generalised epilepsies (serotonin, glutamate, neuropeptide Y, channel blokers such as Ca^{2+}-channel, K^{+}-channel, Na^{+}-channel, Na–H exchanger, glutamate transporter).[16,17] As hormones, via neurotransmitters such as GABA, play a role on seizure recurrences, and that photosensitivity is suppressed by GABA agonists, we may expect to find some changes on PPRs with changing hormonal levels. However, in this study the effect of gonadal hormones on photoparoxysmal responses in cases with IGE cannot be demonstrated. Methodological issues discussed above may account lack of significance. Another explanation is that gonadal hormones have negligible effects on PPRs of IGE patients. In experimental models, estrogen acts as proconvulsant on focal seizures particularly in some brain areas. Clinically, catamenial epilepsy is observed more often in temporal lobe epilepsies compared to extratemporal lobe epilepsies, in left sided temporal lobe epilepsies compared to right sided.[18,19] Other factors such as aging can also change the effects of gonadal hormones. Catamenial pattern becomes more evident by the increasing age in patients with temporal lobe epilepsy. Independent from the cyclic effects of hypothalamopituitary axis, it is claimed that age is effective in modulation.[19] Gonadal hormones have modulating effects on receptors and these effects can be completely variable in different periods of cycle. Various studies indicate that there are factors other than estrogen levels determining the sensitivity of seizures to estrogen.[3] It is observed that estrogen shortens latent period in kainic acid seizures, but that it does not make this effect on flurothyl-induced seizures.[20] In another study it is indicated that even if estrogen has effects in kainic acid induced seizures, it does not have an effect on status epilepticus.[20] Also there are some studies suggesting a possible protecting effect of estrodiol on experimental models.[21] On the other hand, studies regarding the anticonvulsant effects of progesterone indicate more consistent results.[3] It is demonstrated that progesterone administration decreases spike activity on EEG in focal epilepsies.[22] By the aforementioned information it is possible to say that proconvulsant effects of estrogen hormone is variable depending on the type of the experimental model, the seizure, syndrome, localization, lateralisation of seizures, age, genetic features of the individual. Thus, this variability may be used to explain our model, that gonadal hormones have no effect

Table 1
Comparison of number and duration of photoparoxysmal responses (PPRs) during intermittent photic stimulation (IPS) and comparison of spontaneous discharges (number of patients with PPRs during ostrogen phase is 16, during progesteron period is 14).

	Estrogen	Progesteron	Z	p
Duration of PPRs (s)	11.12 ± 14.5	8.63 ± 9.33	-1.15	0.248
Total number of PPRs	5.13 ± 5.03	5.44 ± 4.72	-0.98	0.326
Number of spontaneous discharges	1.64 ± 3.19	1.91 ± 6.36	-0.54	0.587

Table 2
Correlation of PPRs on estrogen and progesterone days with regard to age. r, correlation ratio.

		Age
Duration of PPRs, Estrogen	r	0.240
	p	0.353
Duration of PPRs, Progesteron	r	0.058
	p	0.836
Total number of PPRs, Estrogen	r	0.079
	p	0.763
Total number of PPRs, Progesteron	r	0.065
	p	0.804

on PPRs in female IGE patients. We need further studies to answer this hypothesis.

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