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Lamotrigine and catamenial epilepsy

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Summary Catamenial epilepsy (CE) is characterized by epileptic seizures in the female occurring rhythmatically with the menstrual cycle. Hormonal mechanisms have been proposed as a cause of this epileptic form. Few reports about the efficacy of anti-epileptic drugs (AEDs) have been published. We studied prospectively women with CE who were treated with lamotrigine (LTG) for a period of 3 months in order to evaluate its efficacy, measuring the progesterone levels before and after LTG at the same time. LTG seemed to be efficacious in 66% of women, meaning the disappearance of seizures or reduction of 50% or more of the number of seizures. The reported side effects were few and mild, and the drug was well tolerated. Serum progesterone levels were found to rise during LTG treatment.

Introduction

Catamenial epilepsy (CE) is defined as the occurrence of seizures around the time of menses or an increase in seizures in relation to the menstrual cycle. According to Duncan et al.,[1] the criteria of having at least 75% of the seizures over the 10 days beginning 4 days before menstruation is necessary to fit this description. Herzog et al.[2] defined CE as a greater than average seizure frequency during perimenstrual and periovulatory periods in normal ovulatory cycles and during the luteal phase in anovulatory cycles. Its incidence ranges from 10 to 72% in various studies,[1,3] occurring in perhaps a third of women with epilepsy. It has been postulated that there is correlation between the seizure frequency and estradiol to progesterone (E/P) serum ratio concentration during the menstrual cycle. Recent studies have shown that cyclic changes of ovarian hormones — estrogen (proconvulsive) and progesterone (anti-convulsive) — appear to play a key role in the pathogenesis of catamenial seizures.[4,5] Lamotrigine (LTG) is reported anecdotally to have an effect on catamenial epilepsy. No reports of special efficacy on most of the other frequently used anti-epileptic drugs (AEDs) have been published on this particular group. The use of hormonal, as well as non-hormonal therapy (progesterone and its derivatives, oral contraceptive (OC), acetazolamide, and conventional AED), has been reported

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to have limited efficacy.[6–10] We preformed a prospective study for evaluation of the efficacy of lamotrigine on this patient group.

Experimental/materials and methods

All women suffering from catamenial epilepsy according to the three distinct patterns of CE proposed by Herzog,[2] those with newly diagnosed CE and those patients who had intractable seizures under a first line anti-epileptic drug were included in the study. Excluded were patients who were previously treated with or had allergic reactions to LTG. The study patients completed a bimonthly diary which included details of seizure occurrence and menstruation before starting LTG treatment. Each of the patients underwent MRI examination, as well as EEG. In those patients, who had been under other AED medication and were refractory to their treatment (at least four attacks in every month for the last 2 months), the previous treatment was discontinued and lamotrigine therapy started. In all patients, lamotrigine, as monotherapy, was started with 25 mg daily, and the dosage gradually increased up to 100 mg (b.i.d.). The change of treatment dosage was done according to our protocol for the various AEDs. The progesterone levels were measured twice before beginning LTG treatment during two consecutive months and 3 months after initiating LTG treatment as monotherapy. The progesterone levels were done at day 20–24 in women with ovulation. In women with anovulatory cycles, the progesterone level was taken during the midluteal phase. None of the patients was taking oral contraceptives. The diagnosis of ovulatory or non-ovulatory cycles was made in the gynecological outpatient clinic by using the midluteal phase progesterone level results. The period of follow-up was 3 months.

All serum samples were tested with the same "ECLIA" immunoassay (Elecsys module-COBAS) for measurement of the progesterone levels. Its mean coefficient variation is around 4–5%, having very small variability in the assay results.

Results

Seventy-five women (mean age 31 ± 13.5 years) were evaluated for inclusion into the study. Eighteen patients (mean age 28 ± 8.7; range 22–38 years), three being anovulatory, fulfilled the criteria of CE. The type of seizures included 2 with simple-partial seizures, 11 patients with complex-partial seizures, and 5 with primary generalized tonic–clonic seizures. The mean number of seizures during the last 2 months was 5 ± 3 (range 4–9). Their mean progesterone levels before and during LTG treatment are summarized in Table 1. In six of the study patients, CE was diagnosed at puberty, in eight patients between the ages of 18–25 and in four patients, between the ages of 25–30. Eleven were refractory to one of the AEDs (five on valproic acid and six on carbamazepine) and none of whom being previously treated with LTG, were switched to the study medication. Five patients just newly diagnosed with epilepsy began their treatment with LTG. Two other patients were switched from other AEDs because of adverse side effects (one from topiramate due to confusion, one from phenytoin due to abnormal blood liver tests).

Table 1 Progesterone levels in the study patients with LTG treatment

Patient no.	Before LTG	After LTG
1[a]	0.6	1
2[a]	0.3	1.2
3[a]	0.5	0.8
4	9	11
5	10	11
6	10	10
7	11	13
8	6	12
9	13	16
10	14	13
11	9	12
12	5	9
13	16	18
14	13	13
15	14	12
16	10	13
17	8	10
18	15	18
Mean	9.13 ± 4.96	10.7 ± 4.95

[a] Patients # 1–# 3 are women with anovulatory cycles.

Among the 18 patients treated with LTG, one patient's treatment was discontinued at a dosage of 200 mg due to a skin rash which disappeared after discontinuation of therapy. Three women complained of dizziness and headaches which disappeared within 10 days of treatment. Serum progesterone levels increased during the period of LTG treatment compared to the samples taken during other AED treatment or when under no treatment at all. The change of the mean progesterone serum levels was from 9.13 ± 4.96 to 10.7 ± 4.95 ng/ml ($p = 0.002$). In four women (22%), all seizure attacks disappeared in the follow-up period of 3 months. In a further eight patients, there was a 50% reduction of seizures, respective to the two previous months of

treatment. In six patients, lamotrigine was ineffective. Therefore, concluding that, in 66% of women with CE, LTG was effective with no severe adverse effects, by stopping completely or reducing more than >50% of seizures. There was no difference between the newly diagnosed women and the refractory group of women in regards to the treatment response with LTG.

Discussion

According to the present study, lamotrigine had a beneficial effect of 66% (22% became seizure-free and 44% had a 50% reduction in number of seizures) in the CE cases where the use of the standard AEDs had failed. There are no studies analyzing the efficacy of AED in CE. This effect by lamotrigine can be explained by the fact that this medication is not involved in the dynamic equilibrium changes between estrogen and progesterone during menses. Other AEDs have enzyme-inducing activity and lead to reduced plasma steroid concentration, except for Valproic acid, which is not enzyme-inducing. In the case of patients treated with VPA, another explanation is needed. In our study, less than a third of the patients were on VPA and switched to LTG because of side effects or ineffectiveness. This enzyme action affects estrogen and its metabolites, and in addition, especially acts on progesterone. Morell defined the relationship between lamotrigine in woman with epilepsy and anovulating menstrual cycles as advantageous.[11] The newer drugs, gabapentin and lamotrigine, may have some advantages for women with epilepsy because they do not alter levels of steroids hormones and interfere less with the effectiveness of hormonal contraception. Other theories as rationale for the beneficial effect of lamotrigine on CE in our findings can be attributed to the serum progesterone concentration rise which was observed in our patients having anti-convulsant properties. Adult animal models of epilepsy and clinical evidence suggest that estrogen has excitatory and progesterone has inhibitory effects o neuronal excitability and seizures.[2] The protection of progesterone against seizures in animals is attributed to the reduced progesterone metabolite tetrahydroprogesterone (THP), also known as allopregnanolone, a $GABA_A$ receptor modulating neurosteroid with anti-convulsant properties.[12] There is also a possibility of the presence of increased progesterone level production, as a result of better seizure control. It seems to us that the described cases suggest the probable efficacy of lamotrigine in intractable CE and the importance of understanding its properties for the treatment of these patients, even though the exact mechanism of action is unknown. It is known that AED effectively controls seizures in two-thirds of the epilepsy population, so the favorable outcome of LTG treatment in CE was not completely unexpected. However, a special subpopulation of epileptic women with good efficacy and tolerability with LTG was described. Further expanded studies with more comprehensive hormonal screening are needed to confirm these findings of lamotrigine efficacy in CE as demonstrated in our presented cases.

Conclusions

In our study, using LTG for AED therapy in CE patients was efficacious; a result which was confirmed in other studies when it was given either as add-on or monotherapy. There is a possibility that hormonal factors, especially those of progesterone, may have some influence on women with CE; further studies are needed to investigate this observation.

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