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Effects of Levetiracetam on EEG Activity and Regularity of the Menstrual Cycle in Women Suffering from Epilepsy

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Epilepsy itself and its treatment with anticonvulsants noticeably affect the reproductive function in women suffering from this disease. Levetiracetam (LEV) was shown to be highly effective for the reduction of clinical seizures and EEG epileptic activity. At the same time, its impact on the reproductive/endocrine functions is still unclear. The aim of our study was to evaluate the influence of LEV on the frequency of seizures and epilepsy-related EEG discharges, and also on the regularity of menstrual cycles (MCs) among women with epilepsy (WE) in Georgia. Seizures entirely disappeared in all examined WE with focal and bilateral tonico-clonic seizures (BTCSs), as well as in all cases with juvenile myoclonic epilepsy (JME) ($P = 0.008$). Six months after starting LEV monotherapy, a reduction in single and burst EEG epileptic discharges was observed in all eight women with JME ($P = 0.031$); weakening of burst discharges was also revealed in all patients with focal epilepsy ($P = 0.046$). Among examined WE with regular MCs, oligomenorrhea was observed in two cases from eight patients with focal epilepsy and in one case from seven women with JME treated with LEV. In general, LEV effectively suppresses paroxysmal EEG discharges and also improves clinical seizure control. There was no significant influence of LEV on the MC disturbances, while oligomenorrhea was found in some cases; thus, the respective effects on the MC were at least relatively moderate. More data are needed to establish the level of association between LEV therapy and reproductive endocrine disorders in WE.

Keywords: levetiracetam, epileptic seizures, epilepsy-related EEG phenomena, menstrual cycle.

INTRODUCTION

Epilepsy is a widespread neurological disorder that requires long-term antiepileptic pharmacological therapy. The aim of such treatment is effective control of seizure manifestations without any side effects of anticonvulsants. Unfortunately, the initial antiepileptic drug has been found to be ineffective in approximately half of the patients, and about 35% patients are totally refractory to the used pharmaceutical therapy [1].

It is well known that reproductive endocrine disorders in women, such as menstrual abnormalities, unovulatory cycles, polycystic ovary syndrome (PCOS), and infertility, are two to three times more common in WE than in the general female population [2, 3]. The etiology of these disturbances in WE is multifactorial, including the epilepsy itself and the anticonvulsive medication [4].

In general, the use of antiepileptic drugs is noticeably associated with changes in the serum concentrations of biologically active sex hormones. Some such "old-generation" drugs (phenytoin, phenobarbitone, and carbamazepine) can modulate the activity of hepatic enzymes and activate the production of sex hormone-binding globulin (SHBG), thereby reducing serum levels of biologically active (free) reproductive hormones [5, 6]. On the other hand, hepatic enzyme inhibitors, like sodium valproate (VPA), can increase the levels of active sex hormone, in particular estrogen [7–13], and promote the occurrence of reproductive endocrine disorders characterized by hyperandrogenism and polycystic changes in the ovaries, high serum testosterone concentrations, and disturbances of the menstrual cycle (MC) [14].

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Levetiracetam (LEV) is a relatively new broad-spectrum antiepileptic drug with a mechanism of action different from those of all other drugs. It specifically binds to synaptic vesicle protein (SV2A) in the brain. It is supposed that the anticonvulsive effect of LEV is exerted via modulation of calcium-dependent exocytosis of synaptic vesicles from axon terminals [15]. Pharmacokinetic advantages of LEV include rapid and almost complete absorption, minimal (insignificant) binding to plasma proteins, absence of enzyme induction, absence of interactions with other drugs, and partial metabolism outside the liver [1]. The efficacy of LEV with respect to the reduction of focal [16] and generalized [17] seizures in animal models has been convincingly shown. The effectiveness of LEV is approved as adjunct therapy/monotherapy in patients with focal seizures with/without bilateral tonico-clonic seizures (BTCSs) [18–24], as well as among subjects with generalized seizures of a genetic etiology, especially in the cases with juvenile myoclonic epilepsy (JME) [25–28]. According to recent studies, LEV revealed strong effects on EEG epileptiform patterns via reduction of the frequency of both focal [29] and generalized [30–33] epileptic discharges. As for the side effects of this drug on the reproductive system, a possibility for an effect of LEV on the respective endocrine functions in some animal studies was predicted [34, 35]. According to the data of recent studies, no effect of LEV on estradiol secretion from human granulosa cells was observed. This was reported for both basal or gonadotropin-stimulated conditions and for the effect of LEV on CYP19 aromatase activity after follicle-stimulating hormone (FSH) stimulation [36].

Thus, at present there are few data available for the efficacy and side effects of LEV on the reproductive endocrine function among WE. Thus, we investigated the influence of LEV monotherapy on clinical epileptic events, the respective EEG activities, and the MC regularity in WE of the Georgian population.

METHODS

In this prospective cohort study, women of reproductive age were recruited from persons admitted in the tertiary epilepsy center at the Institute of Neurology and Neuropsychology (INN, Tbilisi, Georgia). Sixteen newly diagnosed cases (eight with focal epilepsy and eight with JME) were included. In these patients, epilepsy was diagnosed according to the International Classifications of Epilepsy (Commission ILAE 2010) [37] by multidisciplinary investigation (neurological assessment, standard EEG recording, neuropsychological testing, and MRI/CT investigation within the framework of the National State Program on Epilepsy). The examined participants were not treated earlier with antiepileptic drugs, were provided with a clear and convincing description of the epileptic events within the preceding three months, and did not take any hormonal treatment/contraception within the last six months prior to the study. Pregnancy, diagnosed endocrine diseases, neuropsychiatric or progressive brain pathologies, cancer (uterus/ovaries/other), mental retardation, an obscure history of epileptic events/menstrual cycles, and violations of the study protocol were the reasons for exclusion from the study.

Additional investigations were performed in all persons of the examined group according to the study protocol. Detailed characteristics of the patients are given in Table 1.

Seizure Frequency. Information on the phenomenology and frequency of seizures prior to the start of investigations was obtined from the patients and related persons. Only detailed and clear descriptions of seizures by a patient and/or an eyewitness were taken into account. During the study, the seizures were recorded using individual calendars; the mean seizure frequency was calculated for the last three months before the admission and during six months since starting the LEV treatment. Seizures were defined as focal with or without loss of consciousness (automatisms, behavioral changes, focal motor, bilateral tonico-clonic) or generalized (myoclonic, absence, tonico-clonic) (ILAE Commission 2010) [37].

Regularity of the MC. Menstrual history (age at the onset of menarche) and the regularity of MCs during the last three months before admission (cycle length and flow amount) were described according to the patient's report. From the start of the study, the patients registered MC regularity in individual calendars during the examination period (six months).

The MC patterns were defined as regular ones (average cycle duration 22 to 35 days), amenorrhea (no menses within more that 6 months), oligomenorrhea (cycle duration more than 35 days), and polymenorrhea (cycle intervals shorter than 21 days) [43–46]. Participants younger than 18 years

met the requirements of the 5th Tanner puberty stage standards at the time of evaluation [47].

EEG Recording and Analysis. EEGs were recorded in all WE before starting the LEV treatment on days 20-22 of the MC (baseline) and, after 6 months since starting of LEV, on the same days of the MC (follow-up). In WE with amenorrhea, disposable EEG investigations on the 1st and 6th months of the study period were planned. At each visit (baseline and follow-up), patients were submitted to ambulatory EEG (A/EEG) recording. The latter lasted 20 min, and recording electrodes were positioned according to the international 10–20 system. Provocation methods used in our study included hyperventilation (HV) and intermittent photic stimulation (IPS) performed according to the international protocols [38].

EEG classification corresponded to that by Luders and Noachter [39, 40]. Epileptic phenomena (spikes, sharp waves, polyspikes, spike-wave complexes, sharp slow waves, and polyspike-wave complexes were classified) as single discharges and/or rhythmic/arhythmic trains/bursts. The time-related definition for single discharges is assessed as their frequency (min^{-1}); for rhythmic trains/bursts we calculated their normalized duration (%) taking the total duration of the bursts within the entire time of recording as 100% [41]. Photoparoxysmal responses (PPRs) were qualified according to the IPS classification of EEG responses [42]

LEV Treatment. Treatment with LEV was begun with a starting dosage of 250 mg/day, with increases of 250 mg/day every sixth day (titration period). Thereafter, the dose regimens were adjusted individually based on clinical estimates of the patient's responses and tolerability. To provide the best seizure control, LEV was given at dosages from 1000 to 2750 mg/day for different patients.

During the a 6-month-long follow-up period, the patients and their relatives were asked to keep a dosage regimen of LEV and to keep a detailed diary of seizures, menstrual history, and normal activity of daily living. Every month, visits to the physician or consultations by phone were realized. No further adjunct therapies were allowed.

Reinvestigations were performed at the end of the follow-up period on the 6th month from the starting of LEV. In all cases, the data on the seizure frequency, EEG investigation, and MC regularity were reevaluated.

Statistical Analysis. Descriptive statistics were used to summarize demographic and clinical data. The Wilcoxon signed-ranks test was used to find differences between paired continuous variables.

T a b l e 1. Demographic and Clinical Characteristics of the Patients

Indices	Focal epilepsy (n = 8)	Generalized epilepsy, JME (n = 8)
Age, years, mean ± s.d. (min–max)	22.1 ± 9.2 (14–40)	17.0 ± 1.6 (15–19)
Age of seizures manifestation, mean ± s.d. (min–max)	18.5 ± 11.1 (5–39)	15.0 ± 1.6 (13–17)
Type of seizures		
Focal seizures only	2	–
Focal seizures with BTCS	6	–
Myoclonia/BTCS	–	8
Etiology		
Genetic	–	8
Unknown	8	–
Febrile sezures	–	–
Family history of epilepsy	–	2
Neurological status		
Normal	8	8
Abnormal	–	–
MRI		
Normal	8	8
Abnormal	–	–
Age of menarche, years, mean ± s.d. (min–max)	12.5 ± 0.5 (12–13)	13.3 ± 1.4 (11–16)
MC regularity		
Regular	8	7
Irregular (amenorrhea)	–	1

T a b l e 2. Characteristic of EEG before and after LEV Therapy

	Focal epilepsy (n = 8)		**Generalized epilepsy, JME** (n = 8)	
	Baseline	LEV follow-up	Baseline	LEV follow-up
Single epileptiform discharges	**4**	**4**	**6**	**3***
Sporadic	1	1	1	2
< 1 min^{-1}	1	2	2	1
1–3 min^{-1}	–	1	2	–
4–6 min^{-1}	2	–	1	–
Rhythmic trains/bursts	**4**	**1***	**8**	**2***
< 1%	1	1	8	2
rare (1–10%)	3	–	–	–

Footnote:* $P < 0.05$ with respect to baseline conditions

The McNemar test was used to investigate association between binary variables. In the comparisons, $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS (IBM SPSS Statistics, Version 21.0, and Armonk, USA).

RESULTS AND DISCUSSION

Evaluation of the Intensity of Clinical Seizures. According to the self-reported clinical evaluation, only one out of two patients with focal epilepsy (who had only focal seizures with or without loss of consciousness) became completely seizure-free after initiation of LEV monotherapy. In the second WE, a clinical adverse effect was noticed in particular, increase in the number of focal seizures and manifestation of BTCS on the 6th month, unlike what was observed within the baseline period.

The total disappearance of seizures was revealed within the LEV follow-up period in all six WE from eight patients with focal seizures and BTCS.

All eight JME WE were seizure-free (having no myoclonic/BTCSs) after starting LEV monotherapy (P = 0.008). In all these patients, no relevant adverse event was manifested during the treatment period.

Evaluation of the MC Regularity. In eight women with focal epilepsy who had normal MCs, some signs of irregular MCs (oligomenorrhea) appeared in two WE, but changes in the mean MC duration in this group within the LEV follow-up period were statistically insignificant (means 32.5 *vs*. 30.5 days).

In the JME group, one woman of seven WE with regular MC showed oligomenorrhea after LEV treatment compared with the baseline. The mean duration of the MCs demonstrated an insignificant LEV-related difference (30.9 *vs*. 28.7 days). An MC disturbance (amenorrhea) was observed in one (17-year-old) patient before admission, as well as after the LEV period.

Evaluation of the EEG Data. According to analysis of the EEG data of WE with focal epilepsy, there were no changes regarding the incidence of single EEG discharges per time within the follow-up LEV treatment period (before in four of eight, after in four of eight patients). At the same time, the reduction of manifestations of burst discharges (in four of eight patients *vs*. one patient), as well as the relevant decrease in the percentage of total duration of a burst (P = 0.046) due to LEV monotherapy were observed.

In eight patients with generalized epilepsy (JME) subjected to LEV monotherapy, manifestations of single discharges within the follow-up period decreased (three of eight *vs*. six of eight patients), and the frequency of single discharges during the treatment period also dropped (P = 0.014). A significant reduction of the appearance (two of eight *vs*. eight of eight, P = 0.031) and total duration of burst discharges (P = 0.014) was observed during the evaluation period.

Photoparoxysmal responses (PPRs) were manifested in five cases out of eight patients with JME under baseline conditions, but such responses were sustained only in one patient at follow-up.

Detailed information on EEG discharges is summarized in Table 2.

The results of our study showed that the positive effect of LEV monotherapy treatment in the WE with focal and generalized epilepsy is quite clear. The total disappearance of seizures in 87.5% of patients with focal epilepsy and in all subjects with JME compared with the respective baseline patterns convincingly confirmed the clinical efficacy of LEV

therapy. These findings are consistent with reports on the effectiveness of LEV as monotherapy in patients with refractory partial seizures [22, 23] and juvenile myoclonic epilepsy [26–28]. However, a clinical worsening in one patient with focal epilepsy manifested as intensification of focal seizures (with or without loss of consciousness) and the appearance of BTCSs during LEV treatment should be mentioned.

In our study, LEV exerted a considerable effect on the manifestation of interictal EEG epileptic burst discharges in WE with focal epilepsy ($P = 0.046$), while any reduction of the incidence of single focal activity was not found in this group. These findings are in agreement with the study of Stodieck et al. [29] where it was reported that LEV induced reduction of interictal epileptic discharges in eight out of 10 patients with focal epilepsy [29].

Levetiracetam is capable of significantly affecting EEG paroxysmal activity and PPRs in WE with JME, which was manifested as a significant reduction in the appearance of single epileptic phenomena ($P = 0.014$) and generalized discharges ($P = 0.031$) compared to the initial state. In four out of five women of the JME group (80%) with PPRs during the baseline period, photosensitivity in the mentioned test was abolished. These data are consistent with published reports concerning remission in paroxysmal EEG discharges, as well as suppression of seizures [24, 30, 31, 38]. Moreover, Specchio et al. [30] showed that epileptiform EEG abnormalities, as well as PPRs, disappeared or decreased markedly in more than 60% of patients during LEV treatment.

As regards the influence of LEV on the MC regularity in WE, we found that irregularities of this cycle (oligomenorrhea) could appear during the above therapy in some patients with focal and generalized epilepsy. However, we did not find significant changes in the mean duration of MC in our examined sampling compared to the baseline indices.

Though there are some studies related to possible LEV effects on the reproductive endocrine hormone levels [34–36], serious clinical endocrine LEV-related problems in humans have not been reported. Our clinical results are, of course, preliminary because of the small dimensions of the examined general WE group and separate subgroups. At the same time, our observations showed that the respective LEV therapy-induced negative effects on the reproductive cycle in WE are at least not dramatic.

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