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Research Letter

Changes in Serum Valproate and Levetiracetam Levels Related to Sex Steroids in Adolescent Girls

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Introduction

In girls with epilepsy, two problems arise after adolescence. First, valproate (VPA), a commonly used antiepileptic drug (AED) in childhood, has been associated with polycystic ovarian changes and reproductive endocrine disorders.[1] Increased body weight with VPA has been suggested as a risk for polycystic ovary syndrome.[2] Second, catamenial exacerbation should be considered in resistant seizures.[3] Catamenial seizures occur in up to 31% of adolescents[4] and are attributed to gonadal hormone fluctuations during the menstrual cycle,[5] but rarely to either fluctuations in AED levels or changes in water and electrolyte balance.[6] In this pilot study, we aimed to show the possible changes in VPA and levetiracetam (LEV) levels during the menstrual cycle and to reveal the effects of serum AED levels on sex steroids. We also compared ovulation and body mass index (BMI) in AED groups.

Materials and Methods

The study was performed after approval by the Human Research Ethics Committee (Karadeniz Technical University, approval number: 24237859/245). Adolescent girls aged between 12 and 18 years, who had menstrual cycles, compliant with VPA (n = 16) and LEV (n = 9) treatments, and without infection, were included in the study. Patients with mental retardation, additional neurological disease, and magnetic resonance imaging findings were excluded. Ovulation was accepted as a progesterone level greater than 5 ng/mL in the midluteal phase.[7] The BMI was calculated as the ratio of weight to height.

Just before the morning dose of AED (between 8 AM and 9 AM), serum estradiol, progesterone, and AED levels were measured in two periods, when the sex steroid levels might be the highest (days 20 to 22, midluteal phase) and the lowest (days one to three, menstrual or early follicular phase) during the menstrual cycle.

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TABLE 1.
Clinical and Demographic Data of the Patients

Demographic and Clinical Features	n (Total 25)
Age (years)	15.4 ± 1.2
Age at epilepsy onset (years)	10.9 ± 3.4
Seizure type (n, %)	
Generalized tonic-clonic	21 (84)
Typical absence	1 (4)
Generalized myoclonic	2 (8)
Focal	1 (4)
Epilepsy duration (years)	5.2 ± 4.7
Treatment	
VPA (n, %)	16 (64)
LEV (n, %)	9 (36)
Patients with ovulatory cycle (n, %)	6 (24)
Patients with anovulatory cycle (n, %)	19 (76)
Menarche age (years)	12.7 ± 0.94

Abbreviations:
LEV = Levetiracetam
VPA = Valproate
Data were presented as mean ± standard deviation.

Analyses were made by a chemiluminescence immunoassay for VPA and sex steroids and by liquid chromatography-tandem mass spectrometry for LEV. Correlations between AED and hormone levels were evaluated by Spearman correlation analysis. Other statistical tests are indicated in the tables. Statistical significance was accepted as P value < 0.05.

Results

The general characteristics of patients are provided in Table 1. Catamenial epilepsy was present in one patient.

Although serum AED levels in the menstrual and midluteal phases were not different, they increased in 68.8% of VPA patients and decreased in 88.9% of LEV patients during the menstrual phase. The rate of decrease in AED level significantly differed in the two groups (P = 0.011). The rate of ovulatory cycles, BMI, BMI z score, and BMI percentiles were not different (Tables 2 and 3).

In VPA patients, a strong positive correlation was detected between serum VPA and progesterone levels, in the menstrual phase (r = 0.731, P = 0.001). Although not statistically significant, estradiol levels showed a positive correlation with VPA and LEV levels, in the same period (r = 0.319 and r = 0.259, respectively, P > 0.05).

TABLE 2.
Comparison of VPA- and LEV-Treated Patients

Parameter	VPA (n = 16)	LEV (n = 9)	P value
BMI (kg/m^2)	22.4 ± 0.95	22.8 ± 1.5	>0.05
BMI z score	0.32 ± 0.23	0.26 ± 0.32	>0.05
BMI percentile	59.8 ± 7	57.4 ± 9.8	>0.05
Treatment duration (years)	4.6 (1.5-8.5)	3 (1.5-6.5)	**0.043**
Patients with an ovulatory cycle (%)	25	33.3	>0.05*
Patients with a decreased AED level in menstrual phase (%)	31.3	88.9	**0.011***

Abbreviations:
AED = Antiepileptic drug
BMI = Body mass index
LEV = Levetiracetam
n = Number of patients
VPA = Valproate
*Fisher exact test, Mann-Whitney U test for those not marked.
Data were presented as mean ± standard error of the mean. Statistically significant P values are marked in bold characters.

TABLE 3.
Comparison of Values During the Menstrual and Midluteal Periods of the Menstrual Cycle in VPA- and LEV-Treated Patients

Parameter	Menstrual	Midluteal	P value
VPA group (n = 16)			
AED level (μg/mL)	72.2 ± 4.87	67.96 ± 4.97	>0.05
Estradiol (pg/mL)	43.5 ± 4.8	193.1 ± 39.8	**0.001**
Progesterone (ng/mL)	0.58 ± 0.1	3.2 ± 1	**0.026**
LEV group (n = 9)			
AED level (μg/mL)	4.55 ± 0.83	6.93 ± 0.94	>0.05
Estradiol (pg/mL)	33.4 ± 3.2	168.4 ± 30.5	**0.008**
Progesterone (ng/mL)	0.41 ± 0.08	2.8 ± 1	**0.021**

Abbreviations
AED = Antiepileptic drug
BMI = Body mass index
LEV = Levetiracetam
n = Number of patients
VPA = Valproate
Data were presented as mean ± standard error of the mean. Statistically significant P values are marked in bold characters. Statistics: Wilcoxon test

Discussion

Our results indicated a strong positive correlation between VPA and progesterone levels during the menstrual phase. We think that one or all of the effects of VPA on progesterone production, metabolism, or at the receptor level, may be the reason for these observed effects. In support of this, VPA has a direct effect on follicular steroidogenesis.[8] In addition, VPA was thought to affect testosterone metabolism, which shares some pathways with progesterone.[9] The absence of this relationship in the midluteal phase may be because of the suppression of luteinizing hormone levels by VPA.[10] No other reports evaluating the effects of levels of both VPA and LEV on levels of sex steroids were found.

There was no difference in the BMI and rate of ovulatory cycles in the VPA and LEV groups. Serum AED levels did not significantly change during menstrual cycle in both VPA- and LEV-treated patients. However, in the menstrual phase, VPA levels increased in most patients, whereas LEV levels mostly decreased. Therefore, we suggest considering this aspect of AEDs in patients with catamenial seizures because of different catamenial patterns.[5]

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