ENDOCRINE REPRODUCTIVE DYSFUNCTIONS IN WOMEN WITH EPILEPSY ON ANTIEPILEPTIC THERAPY

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ABSTRACT

Rationale. The aim of this study is to evaluate sex hormones abnormalities and incidence of polycystic ovary syndrome among young women with epilepsy, analyzing the possible impact of antiepileptic therapy;
Material and methods. In this study we included 41 women with epilepsy, aged between 18 to 40 years, not receiving hormones, with disease duration for 1 to 15 years. The assessment included clinical examination, transvaginal ultrasonography and measurement of sex hormones serum concentration (total testosterone, estradiole, SHBG, LH and FSH) from days 1 to 10 of one menstrual cycle. The patients were compared with a healthy control group. Hormonal data were correlated with the concomitant antiepileptic therapy.
Results. PCO (polycystic ovaries) were found in 19 patients (46%) associated frequently with valproate treatment started before the age of 20 years. PCOS (polycystic ovary syndrome) was found in 20% of the patients, also under valproate therapy. In 22 patients (53%), a high serum testosterone level (19 patients under valproate mono- or add-on therapy). LH/FSH ratio appears bigger than 1 in 21 patients (51%) (17 patients treated with valproate mono- or add-on therapy).
Conclusions. The endocrine - reproductive dysfunctions occurred more frequently in epileptic women treated with valproate; these endocrine abnormalities may have a negative impact on fertility in women with epilepsy and therefore young patients should be screened and carefully evaluated in an endocrinology service prior to start the antiepileptic treatment.

Key words: epilepsy; endocrine – reproductive dysfunctions; antiepileptic drugs

INTRODUCTION

The polycystic ovary syndrome (PCOS) is a condition that affects 5-10% of premenopausal women (1). It is diagnosed by oligo-amenorrhea and clinical (acne, hirsutism) or biochemical hyperandrogenism, after exclusion of other hyperandrogenic conditions. The polycystic ovary (PCO) can be detected with ultrasound and is one of PCOS features (2).

Endocrine – reproductive dysfunctions are found more frequent in women with epilepsy compared with those from the general population. Recent trials have shown that women with epilepsy present more often amenorrhea, oligomenorrhea, irregular or anovulatory menstrual cycles, or untimely menopause (3). Also, these women develop more frequently PCOS (4, 5) whom prevalence in the general population is about 4-7% and *PCO*, with a prevalence of 17 to 22%. The rate of fertility can be reduced in women with epilepsy with 30-60% in comparison with general population.

PCOS is characterized by an increase in LH pulses frequency and amplitude. The level of LH is higher in PCOS than in normal women. An accelerated LHRH-LH pulsatile activity is responsible for the elevated LH levels due to a reduction of hypothalamic opioid inhibition (6).

Several studies have shown that epilepsy itself is associated with an increased incidence of PCOS. The

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impact of seizures on the hormonal constellation is thought to be upon the areas of the brain involved in the circuitry related to the regulation of the hypothalamic – pituitary function (7,8,9).

The increased incidence of PCOS in women with epilepsy treated with valproic acid (VPA) relies on several hypotheses for VPA mechanism in inducing PCOS features: through weight gain which increases insulin resistance, by the absence of induction of hepatic cytochrome P450 enzymes, which could decrease the clearance of gonadal steroids, or VPA may inhibit the conversion of testosterone to estradiole and act as an apoptotic agent in small and medium-sized follicles (10) or increases the androgen biosynthesis (11).

A meta-analysis suggested that VPA alone does not induce changes characteristic for PCOS and that only a multifactorial pathogenic mechanism can explain the associated features of PCOS in epileptic women treated with VPA (12). Another meta-analysis showed a 1, 95 fold increase of PCOS in VPA treated women with epilepsy than in other antiepileptic drugs (AEDs) treated women (13).

SUBJECT AND METHODS

The present prospective study had the objective to identify the sex hormones abnormalities and polycystic ovary/polycystic ovary syndrome among women with epilepsy, treated with antiepileptic drugs. The study group was formed by 41 women diagnosed with epilepsy with generalized or partial seizures taken under observation in the neurology department of Sibiu Emergency Clinical County Hospital.

The patients included in the study were aged 18-40 years, non-users of hormonal - based contraception or other hormonal therapy and did not pose problems requiring medications that interfere with hormone function.

The control group was composed of 20 randomly selected healthy women, aged 18-40 years who were not taking oral contraceptives or other medication that could interfere with the hormonal function and who followed the same clinical features as patients included in the study group.

The clinical study was conducted using a questionnaire that includes anamnestic data (name, age, menstrual cycle characteristics, early menopause, spontaneous abortions, births, fertility, age of onset of the seizures and treatment followed over time, description of seizures, frequency of catamenial seizures, the current treatment) and data of clinical general exam (body mass index, waist-to-hip ratio, hirsutism, acne, hair loss). Hirsutism was evaluated using the Ferriman Gallwey score.

The paraclinical study consisted of biochemical tests and transvaginal or transabdominal ultrasound exams.

The presence of PCO by pelvic ultrasound was established when there were present 10 or more cysts, with a diameter of 2-8 mm and an ovary volume greater than 10 cc. The ultrasound assessment was performed in the early follicular phase, days 1-3 of the menstrual cycle.

We measured hormones concentrations as luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiole, testosterone, sex *hormone* binding globulin (SHBG). The blood samples were collected in the follicular phase of the menstrual cycle, days 1-10 in menstruating women and randomized in women who had amenorrhea for at least 3 months; all the probes were taken in the morning. The biochemical determination of hormones was performed by chemiluminescence technique. The reference values were: LH – 1,1 – 11,6 mUI/l, FSH – 2,8 – 11,3 mUI/l, SBGH – 18 – 114 nmol/l, testosterone – 15 – 80 ng/dl, estradiole – 12 – 160 pg/ml.

The diagnosis of PCOS was established using the criteria of Rotterdam consensus: 2 out of 3 criteria met (oligoovulation and/or anovulation, excess androgen activity, PCO by pelvic ultrasound, exclusion of other hyperandrogenic disease).

In the group of 41 epileptic patients we mainly followed: the frequency of PCO correlated with age, type of seizures, treatment taken over the last year, the initiation of therapy (before or after 20 years), the frequency of PCOS correlated with the type of seizures, treatment taken in the last year, the initiation of therapy (before or after 20 years), the changes in serum hormones (testosterone, estradiole, FSH, LH, SHBG) correlated with antiepileptic drugs (AEDs) administered in the past year, type of seizures.

In this paper we will discuss about the results that concerns some AED and their causality relation with PCOS.

Statistical analysis was performed with EPI-INFO 2000 software. To compare hormonal serum level between two groups we used ANOVA method (a one-way analysis of variance) adapted for small groups and Kruskal-Wallis correction if necessary.

All subjects signed an informed consent and the study was approved by the Local Ethics Committee.

RESULTS

The statistical analysis of the data collected in our study showed that PCO frequency is bigger in the study group than in the control group: 46% vs. 10% (p = 0.02). PCO occurs more frequently in patients with partial seizures (simple or complex) compared with primary generalized seizures: 8 (57.1%) of 14 patients with PCO had partial seizures and 11 (40, 7%) of 27 (p = 0.05) patients with generalized seizures.

Most women with PCOS are treated with Valproate (VPA) monotherapy or associated therapy with enzyme inductor drugs (Carbamazepine, Phenobarbital), also a significant proportion of patients with PCOS are treated with cytochrome P450 enzyme inductor AEDs. A statistically significant association we found just for PCO and VPA monotherapy or associated therapy (p = 0.045) and between PCO and Carbamazepin (CBZ) monotherapy or associated therapy (p = 0.05). Of the 19 patients who presented PCO, in 14 (75%) the therapy was initiated before the age of 20 years. The average age of seizures was relatively the same in the patients with and without PCO, 12,3 years and 12 years (p = 0.81). A significant difference was found in the patients with PCOS (14.5 years) and without PCOS (11.7 years) with statistic significance (p = 0.007) (Table 1).

***TABLE 1**. Average age of the seizures according to pathology*

	With PCO	Without PCO	With PCOS	Without PCOS
Average age of seizures (years)	**12.34**	**12**	**14.5**	**11.7**
	p = 0.81		**p = 0.007**	

From the group of 41 patients, 22 (53.6%) have elevated total serum testosterone (except for patients treated with Lamotrigine (LTG) and Topiramate (TPM)) compared with the control group who did not present increased testosterone (p = 0.000001). Seven (70%) out of 10 patients treated with VPA monotherapy (p = 0.002) and 12 (70.5%) out of 17 patients treated with associated VPA therapy (p = 0.008) have shown elevated levels of total testosterone (Table 2). No patient treated with non-inductor AED showed elevated levels of total serum testosterone. No antiepileptic therapy was statistically significant associated with the increase of FSH (p > 0.05). LH/FSH ratio is known to be a sensitive indicator of reproductive endocrine – disruption (14), so we followed the frequency with which this ratio appears bigger than 1 correlated with medication in the patients included in the study. The number of patients who had LH / FSH with numeric value > 1: 4 (40%) of 10 patients treated with VPA monotherapy (p = 0.2), 2 (40%) of 5 treated with CBZ (p = 0.3), 1 from 1 treated with LTG, 7 (77.7%) of 9 treated with CBZ + VPA (p = 0.04), 4 (80%) of 5 treated with VPA + LTG (p = 0.006), 1 of 1 treated with VPA + TPM, 1 (50%) of 2 treated with VPA + phenobarbital (PB) (p = 0.12), 2 (50%) of 4 treated with CBZ + LTG (p = 0.22). The report was not increased in any patient treated with TPM and/or gabapentin (GBP). There is a significant change in the LH/FSH ratio in patients treated with VPA monotherapy, especially in those treated with VPA + CBZ and VPA + LTG. The results show significant differences between hormonal levels in patients with PCOS compared to those without PCOS only for testosterone (70 ng/dl vs. 52 ng/dl; p = 0.02), estradiole (110 pg/ml vs.

***TABLE 2.** Hormone serum level according to antiepileptic drug use*

Antiepileptic drug	No. of patients	Testosterone (ng/dl)	SHBG (nmol/l)	Estradiole (pg/ml)	FSH (mU/ml)	LH (mU/ml)	LH/FSH > 1 (patients no.)
VPA	10	65,5 (25,7)	37,8 (22,1)	27,6 (11,8)	7,06 (3,71)	7,3 (4,7)	4 (p = 0.2)
CBZ	5	57,9 (23,7)	82,5(53,1)	33,2 (16,4)	7,56 (1,95)	5,82 (2,67)	2 (p = 0.3)
LTG	1	28,2	39,1	157	3,3	10,1	1
TPM	2	32,9 (5,4)	32,5 (24,7)	34,9 (14,9)	7,15 (0,55)	5,75 (0,95)	0
VPA+CBZ	9	59 (18,6)	137,3 (49,7)	143,3 (115,6)	6,25 (2,55)	11,3 (9,55)	7 (p = 0.04)
VPA+LTG	5	56 (10,1)	66,5 (45)	93,2 (62,1)	4,96 (1,6)	6,46 (1,64)	4 (p = 0.006)
VPA+TPM	1	58,6	180	82,1	12,6	14,8	1
CBZ+LTG	4	50,2 (6,7)	75,5 (24,8)	24,55 (4,5)	7,25 (1,85)	6,15 (1,35)	2 (p = 0.22)
PB+CBZ	1	50	2,9	88,3 (103)	9,35 (5,23)	16,38 (20,93)	1
VPA+PB	2	40,8 (3,8)	84,95 (60)	34,7	8,3	9,7	1 (p = 0.12)
TPM+GBP	1	45,7	121	38,2	5,7	5,4	1
Total patients / Mean value	**41**	**55,8 (20,3)**	86,32 (60,52)	72,7 (82,5)	**6,95 (3,27)**	**9,07 (9,02)**	**23**
Reference group	20	32,84 (20,22)	53 (17,8)	34,18 (6,1)	5,66 (1,97)	5.69 (3.2)	4

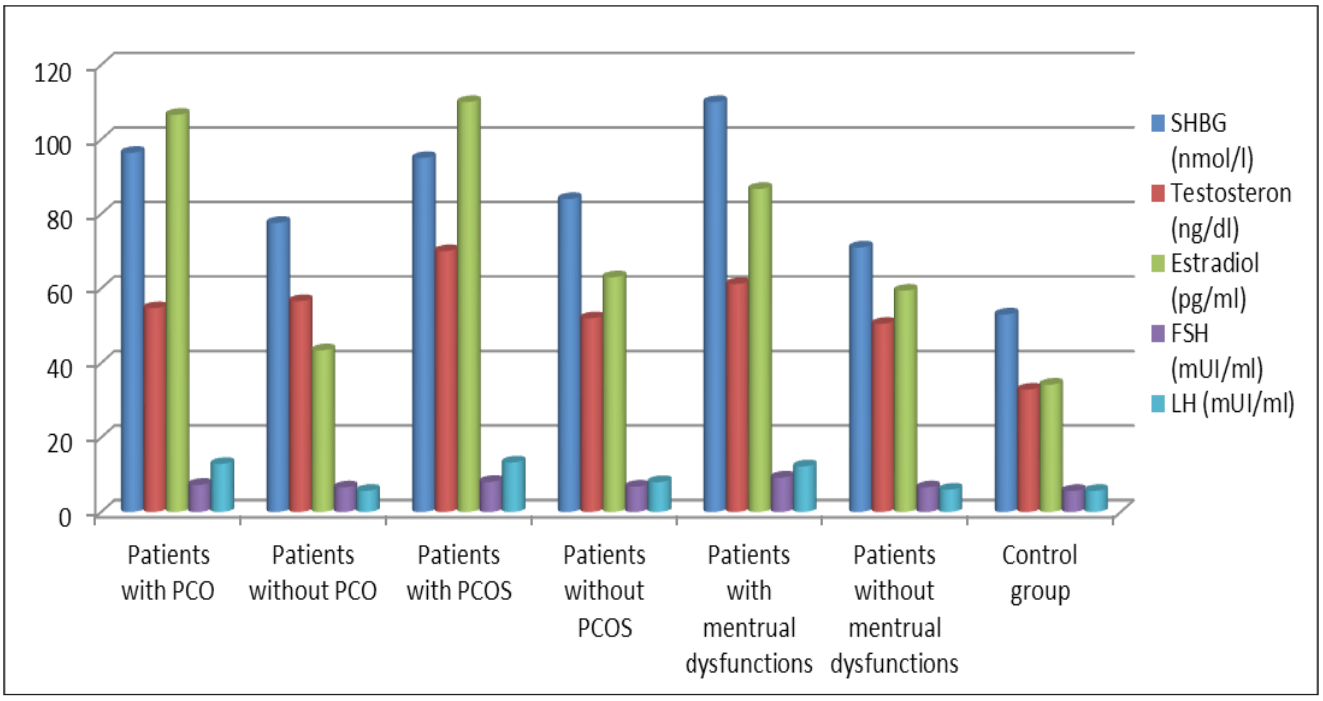

FIGURE 1. *The serum levels of hormones in relation with the pathology found in the study group*

63 pg/ml; p = 0.009) and LH (13.3 mIU/ml vs. 8.03 mIU/ml; p = 0.0075), the serum levels of SHBG and FSH are similar in the two subgroups (Fig. 1).

There are no significant differences between serum level of hormones and seizures type (see Table 3 for details). Calculated p is higher than 0.05 for all hormones.

TABLE 3. *Mean hormonal serum level according to seizures type (standard deviation in brackets)*

Hormone	Patient with generalized seizures	Patient with partial seizures
SHBG (nmol/l)	80 (60,4)	99,9 (58,5)
Testosterone (ng/dl)	59,9 (22,7)	46,6 (8,3)
Estradiole (pg/ml)	74 (87,3)	69,9 (70)
FSH (mUI/ml)	6,8 (2,9)	7,2 (3,9)
LH (mUI/ml)	8,5 (6,1)	10,3 (13,3)

DISCUSSION

Our results suggest that the administration of AEDs during peripubertal period might be an important risk factor in the occurrence of polycystic ovaries. Thus, this study shows that VPA is responsible for PCO by altering plasma testosterone levels (increased), results consistent with other studies (4,15,16). Likewise, the frequency is much higher in comparison with the general population, where asymptomatic PCO present in a percentage exceeding 21%-23% (17). In our study, VPA treatment was associated with a significantly increased level of testosterone. Isojarvi et al. support the hypothesis that VPA may pose a direct effect on ovarian androgen production, or, another hypothesis is that VPA (inhibitor of cytochrome P450) may inhibit ovarian steroid hormone metabolism and thus may increase serum levels of androgens (18,19). As an example, from our study group, a 22 years old woman seizure-free on VPA 1000 mg daily, showed a high level of testosterone of 93.1 ng/dl (normal value, NV = 24 ng/dl), estradiole – 20 pg/ml (NV = 42 pg/ml), SHBG – 69.8 nmol/l (NV = 51 nmol/l), LH – 8.5 mIU/ml (NV = 4.6 mIU/ml), FSH – 5.5 mIU/ml (NV = 6.2 mIU/ml). The transabdominal ultrasound showed multiple ovarian cysts (Fig. 2).

Among classical antiepileptic drugs, VPA, especially VPA + CBZ combination seems to give most of reproductive endocrine disturbances in women, results consistent with the literature (14,20,21,22). Some authors (18,21,23) have suggested that epilepsy itself may affect reproductive endocrine function, or that the endocrine disorders may at least be partly attributed to the use of VPA.

This study weakness is related o the heterogeneity of the study group but also because a control group formed by women with epilepsy but without AED could not be matched. The small number of patients in the study and control groups may have consequences in the significance of our results. We have tried to select as few as possible women in the perimenopause period because of the physiologic hormonal changes (that could interfere with the

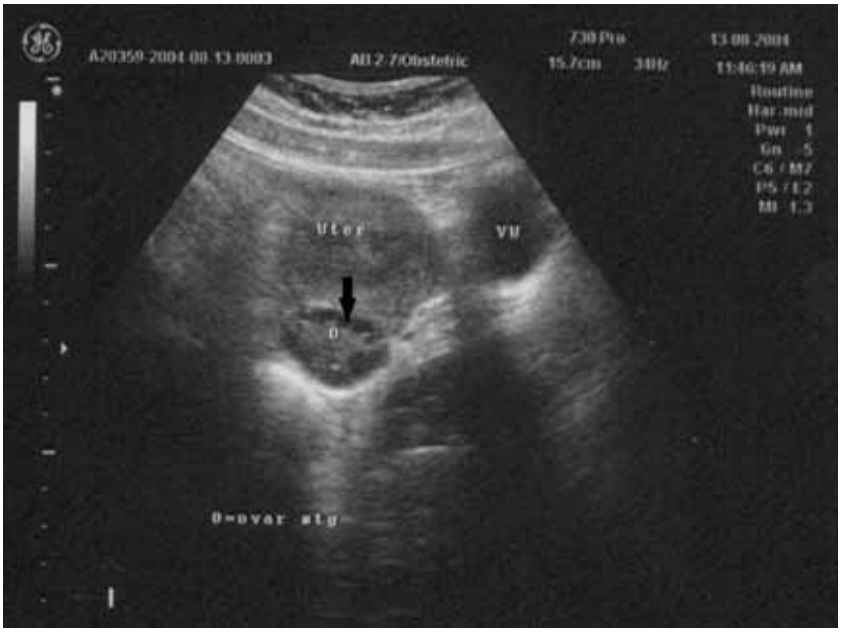

FIGURE 2. *A 22 years old woman with primary generalized seizures on awakening under treatment with VPA, at ultrasound examination presenting polycystic ovaries with numerous cortical cysts better highlighted in the left ovary (black arrow).*

epileptic activity, the elevation of estrogen to progesterone ratio could lead to exacerbation of seizures) that may influence the significance of the hormonal level analysis.

It is therefore clear that larger prospective randomized controlled trials on a more homogenous group need to be done to find a proof upon the direct relation between the AEDs (especially VPA) and reproductive functions.

CONCLUSIONS

On the basis of this study, the results suggest that the administration of these drugs (VPA, or VPA + CBZ) before the age of 20 years and for long periods of time constitute an additional risk factor in the emergence of endocrine and reproductive disorders. New AEDs such as (Levetiracetam, LTG, GBP, TPM) do not appear to induce reproductive endocrine disorders. Regular monitoring of ovarian functions helps in the early detection of reproductive abnormalities in women with epilepsy and could be a useful tool for the choice of the antiepileptic drugs. If adverse effects such as considerable weight gain or menstrual disturbances occur, AED change should be considered.

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