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VALPROIC ACID MONOTHERPAY AND ENDOCRINE ABNORMALITIES IN WOMEN WITH EPILEPSY

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ABSTRACT
Objective: Women with epilepsy have an increased risk of several endocrine disorders. Here we aim to study the prevalence of endocrine disorders, obesity, poly cystic ovarian syndrome and metabolic abnormalities in women on valproate monotherapy. **Methods:** It is a cross sectional study; to study the role of valproate sodium on metabolic measures of convulsive women. We obtained information of 40 patients who were exclusively using sodium valproate. We categorized the patients according to the number of risk factors. **Results**: The patients were stratified according to the number of risk factors, and the variables were compared between groups. There were 10 patients without any risk factor, 20 with one risk factor, and 10 with 2 or more factors for metabolic syndrome. When we compared the studied variables between groups, HDL and HOMA-IR were significantly different between groups, while there were not significant differences between other studied variables. While HDL was negatively correlated with LH in patients without any risk factor ($r=-0.705$, $p<0.05$) it was not correlated with it in patients with one risk factor ($r=-0.017$, $p=0.94$) and was positively correlated with it in patients with two or more risk factors ($r=0.85$, $p<0.001$). **Conclusion:** We showed the role of valporic acid monotherapy on the markers of metabolic syndrome and hormonal status of women with epilepsy. This is the first report reporting the correlation between LH and HDL in patients using sodium valproate monotherapy.

KEYWORDS: Endocrine System Diseases; Epilepsy; Valproic Acid.

INTRODUCTION
Women with epilepsy have an increased risk of several endocrine disorders.[1] Obesity, PCOS, and metabolic bone disease are common side effects of anticonvulsant drugs.[2] While some studies have shown that valporate may have a negative impact on endocrine function, others have shown the contrary. Moreover most of the studies suffer from a number of limitations including the multidrug treatment or short term follow-up. Here we aim to study the prevalence of endocrine disorders, obesity, poly cystic ovarian syndrome and metabolic abnormalities in women on valporate monotherapy.

MATERIAL AND METHODS
It is a cross sectional study; to study the role of valporate sodium on metabolic measures of convulsive women. From the information of the convulsive patients attending Vali Asr hospital of ARAK during January **02**10 to December **022**2, We obtained information on all patients diagnosed with convulsion who were on anticonvulsive treatment for at least 9 months. From them all 40 patients who were exclusively using sodium valporate were selected for further analysis. Exclusion criteria were age older than 40 years old, postmenopausal, treatment with sodium valporate for less than 9 months, using oral contraceptives, medroxyprogestron, hormone replacement therapy or tamoxifen, diabetes, hyperlipidemia, pregnancy in recent 6 months, lactation, using ketogenic diet during study. Convulsion was diagnosed according to the criteria of the American association of epilepsy.[3] Demographic and anthropometric data including age, duration of disease, height, waist circumference, and weight in light clothing and blood pressure in sitting position were recorded. Blood pressure was measured twice after 5 minutes average. The BMI (Kg/m2) was calculated according to the Quetelet formula. All participants gave written informed consent before participation. The research was carried out according to the principles of the declaration of Helsinki; the local ethics review committee of Arak University of Medical Science approved the study protocol. The homeostasis model

assessment of insulin resistance (HOMA-IR) was calculated according to; fasting insulin (μU/ml) × fasting blood sugar (FBS) (mg/dl)/405, as described by Matthews et al. et al.[4]

Blood Samples: Blood samples were collected after almost 12 hours of fasting and serum creatinine, fasting blood sugar (FBS), total cholesterol, triglyceride (TG), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), TSH, T3, T4, FSH, prolactine, testestrone, DHEA and HbA1C were measured. Glucose measurements (intra-assay coefficient of variants [CV] 2.1%, inter-assay CV 2.6%) were carried out using the glucose oxidase method. Cholesterol, HDL, LDL and TG were determined using direct enzymatic methods (Biosystem, Spain). Hormone analysis including TSH, FSH, LH prolactin and free testosterone were performed using Monobind, USA, DHEA-SO was measured using DRG, germany and insulin was measured using Chorous, Italy kits.

Statistical analysis: The statistical package SPSS 16 for windows (Chicago, Illinois, USA), was used for the primary analysis of the cases and controls. Quantitative variables are presented as mean ± standard error of mean (SEM). Qualitative variables are presented as number and percent. Independent sample t test (for quantitative variables) and Chi square test (for qualitative variables) were employed to compare cases and controls. The cut point for HOMA-IR was set at 3.8 as previously suggested.[5] Pearson correlation was also employed to study the correlation between the variables in groups.

RESULTS

The clinical sign and symptoms of the studied patients are presented in table 1. We also categorized the patients according to the FBS (cut point 100 mg/dl), TG (cut point 150 mg/dl) and HDL (cut point 50 mg/dl). The patients were stratified according to the number of risk factors, and the variables were compared between groups. There were 10 patients without any risk factor, 20 with one risk factor, and 10 with 2 or more factors for metabolic syndrome. When we compared the studied variables between groups, HDL and HOMA-IR were significantly different between groups, while there were not significant differences between other studied variables (Table 2).

Correlation: We also studied the correlation of the studied variables with each other in all the studied groups, and also among patients categorized according to the number of risk factors. While HDL was negatively correlated with LH in patients without any risk factor ($r=-0.705$, $p<0.05$) it was not correlated with it in patients with one risk factor ($r=-0.017$, $p=0.94$) and was positively correlated with it in patients with two or more risk factors ($r=0.85$, $p<0.001$).

Table 1: Clinical characteristics of patients

		Number of patients
Age of menstruation (Years)	10	2
	11	1
	12	4
	13	13
	14	7
	15	1
	16	2
Past medical history	0	36
	1	4
Type of drug	0	1
	Valproate	24
	Valproate+others	17
Valproate dose (mg/day)	400	11
	600	15
	800	12
Gravid	0	34
	2	3
	3	1
	5	1
	8	1
Family history diabetes	No	40
	Yes	1
Type of menstruation disorder	No problem	32
	Amenorhea	6
	Polymenorhea	1
History of hypermenorhea	No	34
	Yes	4

Signs and symptoms	No sign	27
	Hirsutism	7
	Acne	1
	Alopecia	2
	Menstruation disorder	2

Table 2: Comparing the studied variables between patients with zero, one or two –four risk factors for metabolic syndrome including FBS, TG, HDL and HOMA-IR.

	Zero (n=10)	One (n=20)	Two-four (n=10)	P value
BMI	23.2± 2.4	22.62±2.41	29.60±4.2	NS
FBS (mg/dl)	83.78±2.4	86.05±1.44	93.30±4.43	NS
GTT	96.33±4.8	98.85±5.47	94.0±5.49	NS
TG (mg/dl)	83.78±6.4	95.25±8.08	125±10.3	<0.05
CHOL (mg/dl)	159.89±5.7	158.85±6.04	175.40±12.31	NS
HDL (mg/dl)	40.22±1.7	56.85±2.4	57.30±6.28	<0.001
LDL (mg/dl)	103.0±5.6	83.0±5.2	180.17±91.8	NS
TSH	2.6±0.56	3.2±0.69	3.20±0.63	NS
FSH	5.53±1.12	8.5±1.6	6.7±0.88	NS
LH	9.04±1.17	62.62±49.31	13.73±2.1	NS
Prolactine	22.7±3.03	28.40±6.2	20.50±4.6	NS
Free testosterone	3.730±1.04	2.67±0.54	2.98±0.4	NS
DHEAS	1.60±0.33	1.57±0.27	1.83±0.31	NS
HOMA	1.87±0.24	1.86±0.30	3.7±0.49	<0.001
Insulin	9.13±1.16	8.80±1.48	16.6±2.3	<0.001

*Variables are presented as mean and standard error of mean. One way ANOVAs was employed to compare the variables between groups. The column of p value is presented for this comparison.

DISCUSSION

Our findings from convulsive women who were on valporate sodium treatment for at least 9 months showed that more than 75% of them have one or more risk factors for metabolic syndrome including hypertension, HDL<40 for men and HDL<50 for women, TG>150 and LDL >100. While we did not found a significant difference between groups in most of the studied variables, HOMA-IR and HDL were significantly different between them. We also showed that while HDL was negatively correlated with LH in patients without any risk factor it was not correlated with it in patients with one risk factor and was positively correlated with it in patients with two or more risk factors. This is the first report reporting the correlation between LH and HDL in patients using sodium valporate monotherapy.

In consistent with our findings, many studies have shown metabolic abnormalities, polycystic ovarian syndrome and hyperandrogenism in women on anticonvulsive therapy.[6-10] However most of them have studied patients on multidrug regimen. While it is known that epilepsy treatment is a risk factor for diabetes and metabolic syndrome. So this could confound the former studies, it is not known whether metabolic syndrome is a side effect of convulsion or the drugs is not known yet.[11, 12] While some studies have shown the role of drugs on these features[13], the others have shown the contrary.[14] Here we studied the patients for at least 9 months and most of the signs and symptoms occurred after the epilepsy treatment.

Our finding demonstrate that HDL and HOMA-IR are significantly different according to the number of risk factors, when we do not observe such a difference between other studied variables. We also showed a positive correlation between HDL and LH in patients with two or more risk factors of metabolic syndrome. This finding is of great clinical importance as LH rise is usually observed in women with poly cystic ovary syndrome and metabolic syndrome. It could be questioned that why HDL is positively correlated with LH in women with risk factors of metabolic syndrome. Lipid abnormalities have been suggested in women on epilepsy treatment.[15] HDL is one of the important factors of metabolic syndrome. Recent studies have shown the ant oxidative properties of HDL.[16] So the positive correlation between HDL and LH may imply the predictive role of HDL in the outcome and future diagnosis of metabolic syndrome in women with epilepsy. We did not found a significant difference in prolactine, TSH, FSH and DHEAS among the studied groups. Other studies have shown that valporic acid disrupts normal neuronal-glial plasticity in the hypothalamus and can thereby cause reproductive neuroendocrine disorders in female patients treated for epilepsy.[17] Previous studies have also reported high levels of DHEAS[18] and prolactine in women with epilepsy.[19]

The principal limitation of the present study is its cross sectional nature which precludes the determination of the direction of causality. We also did not had a control

group to compare the studied variables with them, however it was so hard to find a matched group for this study. On the other hand we took advantage of a relatively large sample size and close similarity between groups in most of the potentially confounding variables.

CONCLUSION

In conclusion for the first time we showed the role of valporic acid treatment on the markers of metabolic syndrome. We also showed that HDL could be a marker of metabolic derangement in women with epilepsy.

CONFLICT OF INTERESTS: None of the authors has any conflict of interest to disclose.

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