

Assessment of Reproductive Changes among Epileptic Patients use Antiepileptic Drugs in Khartoum State (2019)

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Abstract

Background and aim: Epilepsy, antiepileptic drugs, and the reproductive system have complex interactions; this may affect the reproductive function of the women. Accordingly, our study aimed to assess the reproductive changes among epileptic patients on antiepileptic drugs.

Methods: This is analytical case control study. A total of 64 patients fulfilled the inclusion criteria of the study were enrolled in this study, of them 32 diagnosed as epileptic patients on antiepileptic drugs for at least one year (case group), and the other 32 patients were control group, diagnosed with epilepsy but not on antiepileptic drugs. The study was conducted in National Center for Neurological Diseases and sciences, Omdurman Teaching Hospital, Bahri Teaching Hospital and Academic Educational Hospital in Khartoum State, Sudan. Analysis of progesterone, follicular stimulating hormone, luteinizing hormone and testosterone hormone were done by ELISA KITS.

Results: A total number of 64 patients were analysis during the study period in case 47% is males and 53% is females in control 62% is males and 38% is females. The study showed that among the patients used carbamazepine, valproate and phenytoin there was significant decrease in mean plasma concentration of testosterone hormone (2.49 ± 1.58) and follicular stimulating (6.47 ± 2.94) and progesterone (1.83 ± 0.67) with p-value (0.012), (0.054), (0.091) respectively, when compared with mean of control group of testosterone hormone (4.14 ± 3.24), follicular stimulating (7.99 ± 3.28), progesterone (2.21 ± 1.08). There was significant increase in mean plasma concentrations of

luteinizing hormone (13.1 ± 8.74) with p-value (0.000) when compared with mean of control group (3.83 ± 1.59). From data suggest that antiepileptic drugs have effect on reproductive hormones.

Conclusion: The study concluded that antiepileptic drugs in women had significant effects in lowering the levels of reproductive hormones among women with epilepsy and on antiepileptic drugs for at least one year.

Keywords: EEG Electro encephalography, PHT Phenytoin, VPA Valproic acid, CBZ carbamazepine

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1. Introduction

Reproductive endocrine disorders are more common among patients with epilepsy than among the normal population [1]. Changes in female hormones that may result in menstrual irregularity, reproductive problems, and abnormalities of bone health [2].

Hormonal alterations, including changes in prolactin, follicle-stimulating hormone and luteinizing hormone have been observed following generalized and focal seizures [1]. They are thought to arise as a result of connections between the hypothalamic-pituitary axis and areas of the brain involved in seizures, although the precise mechanisms are unclear. These hormonal problems can result in reproductive dysfunction, with the most common disorders being polycystic ovarian syndrome (PCOS) and hypothalamic amenorrhoea [1,4]. It is estimated that PCOS occurs in 20% of women with epilepsy, compared to 5% of those without [2].

Reduced potency, diminished libido, erectile dysfunction, lack of sexual satisfaction, and sperm abnormalities have been found in men [3][4][5]. In both sexes, sexual problems [6] and endocrine changes have been frequently described in previous studies [7][8]. These

disorder have attributed to epilepsies itself and AEDs. The current study aimed to assess the reproductive changes among epileptic patients on antiepileptic drugs.

2. Materials and Methods

2.1 Study design: This is analytical case control study.

2.2 Study area: The study was conducted in national center for neurological diseases and sciences, Omdurman Teaching Hospital, Bahri Teaching hospital and Academic Educational Hospital at Khartoum State, Sudan.

2.3 Study period: The study starts in June 2019- August 2020

2.4 Study population: Adults male and female attended to the clinics that have epilepsy and receiving antiepileptic drugs for at least one year, and adults male and female attended to the clinics have epilepsy and not receiving antiepileptic drugs.

4.4.1 Inclusion criteria: Adults male & female who were diagnosis as epileptic based on EEG and use antiepileptic drugs for more than one year, epileptic patients who received one of the following antiepileptic drugs (carbamazepine, sodium valproate or phenytoin) from at least 1 year and accepted to participate in the study were selected.

2.4.2 Exclusion criteria; Patients who have mental retardation or history of any hormone disturbance, women take hormone contraceptive, patients how refuse to give consent, women take estrogen or progesterone therapy, pregnant women, male working in hot or cold environment, any patient is diagnosis before have defect in thyroid hormone or prolactin hormone, any none Sudanese patient were excluded.

2.5 Sample: The sample was calculated according to the know formula which is used to reach a certain desired margin of error in the results. The sample size in this study was calculated for each category (on average) to give a maximum of error (0.05) with probability of ($\alpha=0.05$) as follow;

$$N = z^2 \times p \times q / d^2. N = 3.3124 \times 0.025 \times 0.975 / 0.0025 = 32.2$$

Z= the value in normal curve corresponding to level of confidence 95%=1.96.

P=probability prevalence in the community is (highest prevalence reported in Khartoum 2.5%) or 0.025. Q=(1-p) =1-0.025. D= margin of error =0,05.

Data collection: Data was collect by researcher in rest time of patient, collect by using a questionnaire in stander conditions by use gloves, mask and new syringe, if have any emergences case I have doctor to see him, and explain the study procedures and measurements to the volunteers, the blood sample will be collected in a plain container, 5

ml from each patient will separate to plasma by centrifugation technique. Plasma was frozen at $-20\text{ }^{\circ}\text{C}$ and stored in the research laboratory in AL-Neelain University till completed collection. Hormones' levels were analyzed using ELISA technique in Al-Neelain University faculty of medical laboratory sciences.

2.8 Statistical analysis: Data was analyzed using Statistical Packages for Social Sciences (Version 25.0). T test was used to compare between mean values of reproductive hormones and P value regarded significant if < 0.05 (CI 95%).

2.9 Ethical consideration: Permission of this study obtained from Ministry of Health Khartoum state and from Al-Neelain University also written consent was tacked from hospital and all participants. Research purpose and objectives was explained to participant in clear simple word. Participants have voluntary to give informed consent. Questionnaire was filled with the participant in their rest time without any interruption to their work.

3. Results

Table (1) mean comparison of study parameters in case versus control groups

Parameters	Case (Mean \pm SD)	Control (Mean \pm SD)	<i>P-value</i>
Testosterone	2.49 \pm 1.58	4.14 \pm 3.24	0.012
FSH	6.47 \pm 2.94	7.99 \pm 3.28	0.054
LH	13.1 \pm 8.74	3.83 \pm 1.59	0.000
Progesterone	1.83 \pm 0.67	2.21 \pm 1.08	0.091

The table shows the mean \pm standard deviation and probability (p)

Independent t-test used for comparison

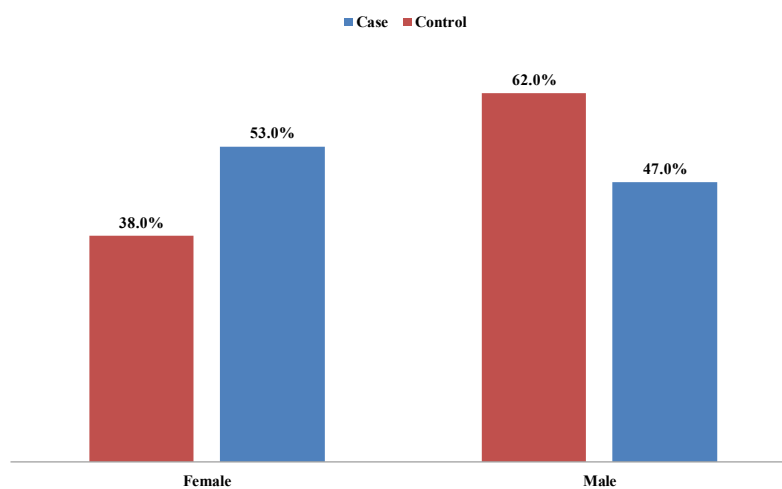
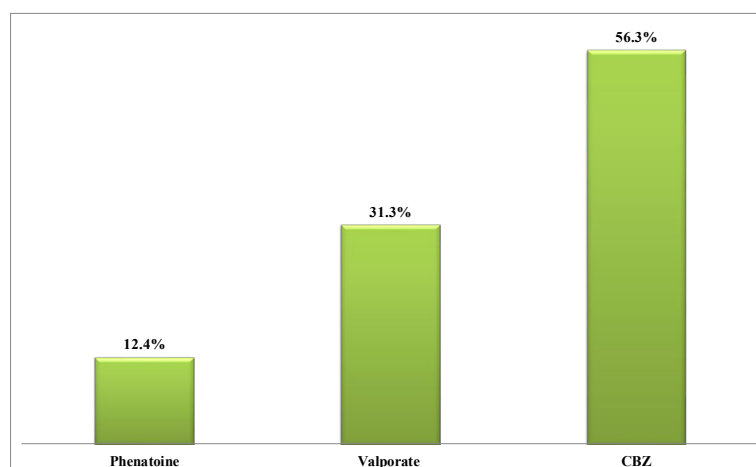
P-value ≤ 0.05 is considered significant.

Table (2) mean comparison of study parameters across gender

Parameters	Male (Mean \pm SD) n=15	Female (Mean \pm SD) n=17	<i>P-value</i>
Testosterone	2.93 \pm 1.93	2.11 \pm 1.11	0.146
FSH	6.56 \pm 3.48	6.38 \pm 2.48	0.868
LH	7.08 \pm 5.94	18.5 \pm 7.27	0.000
Progesterone	2.13 \pm 0.55	1.56 \pm 0.68	0.016

Table (3) mean comparison of study parameters across type of drug use

Parameters	Mean±SD			<i>P-value</i>
	Cbz n=18	Valborate n=10	Phenotoin n=4	
Testosterone	2.31±1.43	2.06±0.92	4.38±2.48	0 .030
FSH	5.97±2.99	6.62±1.98	8.30±4.58	0.364
LH	13.2±8.01	15.9±10.3	5.65±1.86	0.142
Progesterone	1.58±0.69	2.08±0.58	2.27±0.45	0.042

**Figure (1) distribution of study group according to gender.****Figure (2) distribution of study group according to type of drug used.**

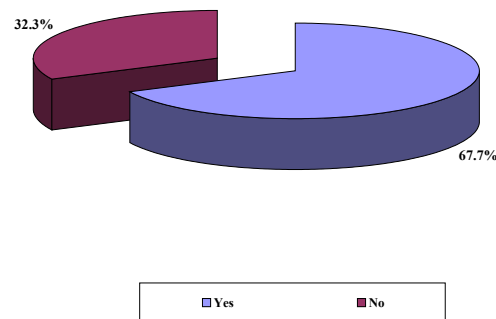


Figure (3) distribution of study group according to male loss of libido.

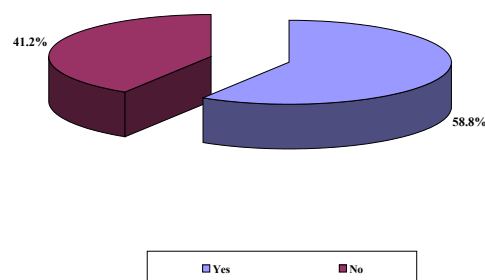


Figure (4) distribution of study group according female defect in menstrual cycle.

4. Discussion

Epilepsy had potential effects on reproductive function among women diagnosed with epilepsy and on antiepileptic drugs. To test the reproductive change among epileptic patients on antiepileptic drugs, a total of 64 patients were enrolled in this study. The patients divided into two groups, the first group was the cases included 32 patients diagnosed as epileptic patients on antiepileptic drugs for at least one year and the second group was the control group included 32 patients diagnosed with epilepsy but

not on antiepileptic drugs. Within case group male to female ratio was 0.8: 1, while among control group this ratio was 1.6: 1 (Figure 1). Within cases, loss of libido reported in 67.7% of males (Figure 2). On the other hand, defects of menstrual cycle reported in 58.8% of females (Figure 3). Sahota, et al reported that menstrual abnormalities were observed in 83 of 427 (19.4%). Asian women with epilepsy on antiepileptic drug irrespective of epileptic seizure type; of these, 50 (60.2%) received valproate, 21 (25.3%) received carbamazepine, 11 (13.3%) received phenytoin, and one (1.2%) received phenobarbitone as the primary AED. Almost half of valproate-treated women had significant weight gain and obesity [9].

Among cases 56.3% used CBZ, 31.3% used valproate and 12.4% used phenytoin (Figure 4). The Mean \pm SD value of testosterone among cases was 2.49 \pm 1.58 which is significantly lower than the mean values among control (4.14 \pm 3.24; P = 0.012 < 0.05), while the mean value of FSH and progesterone were 6.47 \pm 2.94 and 1.83 \pm 0.67 respectively, cases compared to (7.99 \pm 3.28 and 2.21 \pm 1.08) respectively, among control (there is no significant difference, P values > 0.05). On the other hand, the mean value of LH was 13.1 \pm 8.74 within case group compared to 2.11 \pm 1.11 within control group (P value = 0.000 < 0.05) (Table 1). These values indicate that epilepsy accompanied with use of antiepileptic drugs significantly lower the values of testosterone and LH hormones, while no prominent effect observed regarding FSH and progesterone. Our study showed that within males the mean value of testosterone and FSH were 2.93 \pm 1.93 and 6.56 \pm 3.48 respectively and these values among females were 2.11 \pm 1.11 and 6.38 \pm 2.48, indicates insignificant differences between males and females in these parameters (P value > 0.05). When considering the levels of LH and progesterone, the findings of this study revealed that the mean values of the LH was significantly higher among females and progesterone significantly higher among males (P values 0.000 and 0.016 < 0.05) (Table 2). Lossius, et al found that reversible endocrine changes in sex steroid hormone levels could be observed in both sexes after withdrawal of AEDs. For CBZ, which was the drug used by the majority of the patients, withdrawal led to significant increases in serum testosterone concentrations and free androgen index (FAI) in both men (n = 19) and women (n = 19). Mean differences in change in FAI between the withdrawal group and non-withdrawal group were in men 17.49 (CI 10.16–24.81, p \leq 0.001), and in women 1.61 (CI 0.62–2.61, p \leq 0.001) [10]. Löfgren, in her study reported that reproductive disorders were more common in women with idiopathic generalized

epilepsy and in women taking valproate. Also young age increased the risk of these disorders. Oxcarbazepine was associated with reproductive disorders in women with epilepsy. In men all antiepileptic drugs studied were associated with sperm abnormalities, and sperm abnormalities in men taking valproate were associated with decreased testicular volume [11].

Regarding the effect of antiepileptic drugs on reproductive function of the patients in terms of levels of testosterone, FSH, LH and progesterone, the findings of our study revealed that the mean values of testosterone among patients on CBZ, Valborate and phenytoin were 2.31 ± 1.43 , 2.06 ± 0.92 and 4.38 ± 2.48 respectively (P value = $0.030 < 0.05$), and progesterone mean values were 1.58 ± 0.69 , 2.08 ± 0.58 and 2.27 ± 0.45 respectively, (P value = $0.042 < 0.05$) indicate that CBZ and Valborate had higher effect in lowering the values of these two parameters compared with phenytoin. On the other hand, the mean values (see Table 3) of FSH and LH were not significantly different between the cases and control groups (P values > 0.05). Similar to Mohamed et al who reported that among Egyptian patients on antiepileptic drug there was significant decrease in luteinizing hormone and follicle-stimulating hormones and highly significant increase of prolactin serum level. Isojärvi, concluded that valproate (VPA) medication may have effects on serum androgen concentrations and it reduces serum follicle stimulating hormone levels in men with epilepsy. However, the clinical significance of the VPA related reproductive endocrine changes in men is unknown. On the other hand, in women the use of VPA is associated with a frequent occurrence of reproductive endocrine disorders characterized by polycystic changes in the ovaries, high serum testosterone concentrations (hyperandrogenism) and menstrual disorders. Young women with epilepsy seem to be especially vulnerable to the effects of VPA on serum androgen levels [12].

5. Conclusion: The study revealed that antiepileptic drugs in women had significant effects in lowering the levels of reproductive hormones among women with epilepsy and on antiepileptic drugs for at least one year.

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