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Effects of carbamazepine on male reproductive hormones

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Abstract

Background: Reproductive endocrine disorders and sexual dysfunction are common among men with epilepsy. We investigated sexual hormone serum levels among men with newly diagnosed epilepsy, before starting any antiepileptic drug (AED), and then after starting carbamazepine (CBZ), to determine the role and effects of epilepsy versus CBZ in creating reproductive endocrine disorders.

Methods: In this prospective study, male patients 20 to 40 years of age who due to new-onset seizure(s) were referred to the outpatient epilepsy clinic at Shiraz University of Medical Sciences from 2009 through 2012 were studied. A blood sample was obtained to evaluate the serum levels of follicle stimulating hormone, luteinizing hormone, prolactin, testosterone, free-testosterone, dehydroepiandrosterone sulfate and sex hormone binding globulin. CBZ was started after blood works. After at least three months of taking CBZ, another blood sample was obtained to determine the serum levels of those hormones again.

Results: Twenty patients were included. Their mean age (± standard deviation) was 28 years (± 5). The statistical analysis with paired sample tests did not show any significant changes in serum levels of sex hormones before and after CBZ therapy.

Conclusion: Despite the fact that, sexual dysfunction and reproductive disorders are common among men with epilepsy, the exact pathophysiology of these problems is not clear yet. Further studies are required to determine the exact role of epilepsy itself, AEDs, and other possible determinants.

Keywords: Carbamazepine, Epilepsy, Sex hormone, Men.

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Introduction

Reproductive endocrine disorders and sexual dysfunction including diminished libido and potency are more common among men with epilepsy than in the general population (1-5). Both epilepsy and antiepileptic drugs (AEDs) may play a role in creating these problems, however the underlying mechanisms have not yet been identified clearly (4, 5). Carbamazepine (CBZ), phenytoin (PHT), valproate (VPA), and oxcarbazepine (OXC) have been associated with sexual dysfunction in various studies (1-5). However, separating the direct effects of epilepsy versus AEDs has always been difficult (6).

In this study, we investigated sexual hormone blood levels among men with newly diagnosed epilepsy, before starting any AED, and then after starting CBZ, to determine the role and effects of epilepsy versus this antiepileptic drug in creating reproductive endocrine disorders in these patients.

Methods

In this prospective study, male patients who due to new-onset seizure(s) were referred to the outpatient epilepsy clinic at Shiraz University of Medical Sciences,

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from 2009 through 2012, were studied. Inclusion criteria were age 20 to 40 years at the time of referral; epileptic nature of seizure(s) (based on the clinical grounds and the electroencephalographic and/or imaging studies); no use of even a single dose of any antiepileptic medication (including even a stat dose of any antiepileptic drug) before their first visit; and not having any other previous medical or psychological disorders requiring long-term treatment. Out-patient electroencephalography (EEG) and brain magnetic resonance imaging (MRI) tests were performed in all patients at the time of referral. After determining the nature of their epilepsy and when we considered that CBZ is an appropriate drug for their condition (7), we discussed with the patients the study procedures and our purposes. When they signed the informed consent forms, a blood sample was obtained to evaluate the serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), testosterone, free-testosterone, dehydroepiandrosterone sulfate (DHEAs) and sex hormone binding globulin (SHBG), in the morning (at 8 am) and fasting state. Prolactin, FSH, LH and SHBG were assayed by immunoradiometric assay (IRMA) systems. We used Prolactin IRMA kit (Beckman Coulter Company-Czech Republic), hFSH (^{125} I) IRMA kit, hLH (^{125} I) IRMA kit and SHBG (^{125}I) IRMA kit (Institute of Isotopes Co., Budapest, Hungary).The testosterone level was measured by RIA using commercially available reagents from Immunotech (Beckman Coulter, Marseille, France). Serum free testosterone level was measured by ELISA (Enzyme-linked immunosorbent assay) kit (diagnostics Biochem Canada Inc.). DHEAs was measured by a commercial RIA kit (Immunotech Beckman Coulter, Marseille, France).Reference values for adult male were as follows: prolactin: 1.0-18ng/ml; LH: 1.9 – 9.4mIU/ml; FSH: 1.0-10.5mIU/ml; testosterone: 3-12ng/mL; Free testosterone: 3.84-34.17pg/ml; DHEAs: 1.3- 4.4µg/ml; and SHBG: 7.7–81nmol/l.

Carbamazepine was started after blood works with 200 mg per day and titrated to 400-600 mg per day in 1-2 weeks. Our strategy was to prescribe CBZ 400 mg per day in patients with a single seizure who were willing to take medicine and administer CBZ 600 mg per day in patients with more than one seizure before their referral. After at least three months of taking CBZ, another blood sample was taken under the same condition (in the morning (at 8 am) and fasting state) to determine the serum levels of those hormones again.

Statistical analyses were performed using paired sample tests to determine potentially significant differences, and a p value less than 0.05 was considered as significant. This study was conducted with approval by Shiraz University of Medical Sciences Review Board and the Ethics Committee.

Results

During the study period, 20 patients were included. Their mean age (± standard deviation) was 28 years (±5). The minimum age was 20 years and the maximum 40 years. Clinical findings of these patients are summarized in Table 1.

Thirteen patients had focal epilepsy based on their clinical, EEG and / or MRI findings. Seven patients had unclassified epilepsy. None of these seven patients had history of absence or myoclonic seizures and family history of epilepsy was negative among all of them. Four patients had a single seizure; we prescribed CBZ 400 mg per day in these patients. Sixteen patients had more than one seizure before their referral; they received CBZ 600 mg per day. The statistical analysis using paired sample tests did not show any significant changes in serum levels of sex hormones before and after CBZ therapy (Table 2).

In individual assessments, one patient had abnormally low serum FSH level (0.8mIU/ml) before CBZ therapy; it remained low after CBZ therapy (0.9mIU/ml). No one had abnormal LH serum levels before and after CBZ therapy. PRL was abnormally high in one patient before and after CBZ therapy (28.7 and 26.4ng/ml, respectively).

Table 1. Clinical characteristics of the patients studied

	EEG	Brain Imaging	Final diagnosis	Carbamazepine dosage mg / day
1	Left midtemporal spike	Left frontal cystic lesion	Focal epilepsy	600
2	Normal	Right frontal encephalomalacia	Focal epilepsy	400
3	Normal	Left parietal old ischemic changes	Focal epilepsy	600
4	Normal	Non-specific white matter changes	Unclassified epilepsy (UE)	600
5	Normal	Normal	UE	600
6	Normal	Normal	UE	600
7	Right temporal polymorphic delta activity	Right temporal atrophy	Focal epilepsy	600
8	Normal	Right parieto-occipital gliosis	Focal epilepsy	400
9	Left central spikes	Normal	Focal epilepsy	600
10	Normal	Left frontal encephalomalacia	Focal epilepsy	600
11	Right anterior temporal spikes	Right mesial temporal sclerosis	Focal epilepsy	600
12	Normal	Normal	UE	600
13	Left midtemporal sharp waves	Left mesial temporal sclerosis	Focal epilepsy	600
14	Normal	Normal	UE	600
15	Normal	White matter disease	Focal epilepsy	600
16	Left anterior temporal sharp waves	Left temporal focal cortical dysplasia	Focal epilepsy	600
17	Normal	Normal	UE	400
18	Normal	Left mesial temporal sclerosis	Focal epilepsy	400
19	Normal	Right frontal encephalomalacia	Focal epilepsy	600
20	Normal	Normal	UE	600

Generalized tonic-clonic (GTC); complex partial (CP); Unclassified epilepsy (UE).

Table 2. Sex hormones before and after carbamazepine therapy in men with epilepsy (Statistical analysis: paired sample tests)

		Paired Differences					Sig. (2-tailed)
		Mean	Standard Deviation	Standard Error Mean	95% Confidence Interval of the Difference Lower	Upper	
Pair 1	PreFSH – postFSH	-0.03000	0.97176	0.21729	-0.48480	0.42480	0.892
Pair 2	PreLH – postLH	-0.16500	1.78275	0.39863	-0.99935	0.66935	0.684
Pair 3	PrePRL – postPRL	0.11500	2.97592	0.66544	-1.27777	1.50777	0.865
Pair 4	Pre Testosterone – post Testosterone	0.08300	3.05987	0.68421	-1.34907	1.51507	0.905
Pair 5	Pre DHEAs – post DHEAs	0.22000	0.93110	0.20820	-0.21577	0.65577	0.304
Pair 6	Pre Free Testosterone – post Free Testosterone	0.45450	4.07895	0.91208	-1.45451	2.36351	0.624
Pair 7	PreSHBG – postSHBG	2.92500	17.44531	3.90089	-5.23966	11.08966	0.463

Follicle stimulating hormone (FSH); luteinizing hormone (LH); prolactin (PRL);dehydroepiandrosterone sulfate (DHEAs); sex hormone binding globulin (SHBG).

Total testosterone was high before and after CBZ therapy in one patient (12.9 and 12.1, respective ly); after CBZ therapy, in two patients it increased to abnormally high levels (8.7 to 15.2 and 11.7 to 15.5ng/ml, respectively) and in one it decreased to abnormally low level (14.3 to 8.3ng/ml). Free testosterone decreased to abnormally low level in one patient (11.2 to 2pg/ml), after CBZ therapy. DHEAs was below minimum expected level in four patients, before and after CBZ therapy; decreased to abnormally low levels in seven and increased from abnormally low levels to the expected levels in four patients. It was not abnormally high in anyone, either before or after CBZ therapy. SHBG was above the maximum expected value before CBZ therapy in two patients; it decreased to the expected range in both patients after starting CBZ therapy (from 109 to 62.3 and from 93.2 to 48.7nmol/l).

Discussion

Reproductive disorders are unusually common among men with epilepsy. Diminished libido or potency occurs in approximately 20% of men with epilepsy (5, 8). The etiology of hypogonadism and reproductive and sexual dysfunction in men with

epilepsy has been attributed to a number of possible etiologies; including psychosocial stress, AEDs, and epilepsy itself (8).Psychosocial stress associated with epilepsy may play an important role in hypogonadism; however this needs further investigation. Separating the direct effects of epilepsy versus AEDs has always been difficult. Role of AEDs in sexual dysfunction among patients with epilepsy has been investigated repeatedly. It has been speculated that AEDs can induce various hormonal abnormalities; in particular, the use of the liver enzyme inducing AEDs, such as phenobarbital (PB), PHT and CBZ, which increases serum SHBG concentrations. This increase leads to diminished bioactivity of testosterone, which may result in diminished potency and thus reduced fertility (9).In one study, the investigators compared the sexual function and reproductive hormone levels among men with epilepsy who took various AEDs, untreated men with epilepsy, and normal controls (5). Eighty-five men with focal epilepsy (25 on CNZ, 25 on PHT, 25 on lamotrigine (LTG), and 10untreated for at least 6 months) and 25 controls were studied. Sexual function scores (S-scores), hormone levels, hormone ratios, and gonadal efficiency were compared among the five groups. S-scores, bioactive testosterone levels, bioactive testosterone/bioactive estradiol, and bioactive testosterone/luteinizing hormone were significantly greater in the control and LTG groups compared to the CBZ and PHT groups. SHBG was significantly higher in the CBZ and PHT groups compared to all other groups. Bioactive testosterone declined with age and was significantly greater among men with epilepsy than among controls and notably greater in the CBZ and PHT groups than in the LTG and untreated groups. The authors concluded that the sexual function, bioavailable testosterone levels, and gonadal efficiency in men with epilepsy who took LTG were comparable to control and untreated people and significantly greater than those with CBZ or PHT treatment (5). In another previous study, 20- 40 years old men with epilepsy, taking either VPA (n=16) or CBZ (n=19) as monotherapy for more than two years were included and compared with age-matched controls. It was observed that long-term CBZ treatment leads to significant lower testosterone / SHBG ratio (10).In another study, the authors investigated the reproductive and sexual function in 18- 45 years old men and women with epilepsy treated with levetiracetam (LEV: 30 men/26 women), CBZ (63 men/30 women), or LTG (37 men/40women) monotherapy and in healthy controls (36 men/44 women). In men, no drug-specific hormonal pattern was observed after LEV treatment. Male patients in all treatment groups had lower androstenedione and free testosterone. Those using CBZ had lower free androgen indices and DHEAS levels, and higher SHBG, FSH, and LH levels (11). In one study, the authors measured 26 unconjugated steroids, 18 steroid polar conjugates, gonadotropins and SHBG in six patients taking VPA and 11 taking CBZ monotherapy, and in 19 healthy adult men. Decreased testosterone, free androgen index, free testosterone, dehydroepiandrosterone, and DHEAS levels were associated with epilepsy per se. Valproate therapy increased 5-dihydrotestosterone, androsterone, epiandrosterone, dehydroepiandrosterone, and DHEAS levels. Carbamazepine induced only slight decrease in isopregnanolone, 5α, 20α-tetrahydroprogesterone, and androstanediol levels (12). However, to the best of our knowledge, the current study is the first pre / post AED study in the literature. In the current study, we observed no significant change in sex hormones after prescribing CBZ to the patients with epilepsy. This is in contrast to most previous studies, which compared patients with epilepsy to healthy control groups (not to their own status before starting AED!). In our study, two patients had high SHBG levels before starting CBZ therapy. No one had high levels after treatment with CBZ. Therefore, the observed high SHBG levels and other hormonal imbalances observed in

previous studies could be due to epilepsy itself rather than AED consumption. Our findings might indirectly emphasize the role of epilepsy itself in causing sexual dysfunction. The limbic system is one of the most common sites of epileptogenesis in epilepsy in adults. It also has integral role in reproductive endocrine regulation and in sexual and reproductive function (8). In a previous study, the authors investigated the existence of neuroendocrine dysfunction in patients with temporal lobe epilepsy by comparing the response of serum LH levels with intravenous LH-releasing hormone infusion in patients with epilepsy and normal controls. Five of seven consecutive patients had response curves that fell almost entirely outside of the normal control range, and all seven had either baseline or peak values that were outside of the normal range. They suggested that hypothalamic-pituitary control of gonadotropin secretion may be altered among patients with temporal lobe epilepsy (13).In two previous studies, successful temporal lobectomy in hypogonadal men with intractable seizures were associated with normalization of testosterone levels (14) and improvement in sexual interest and function (15). Bauer and his colleagues studied 22 men with temporal lobe epilepsy aged 25 to 48 years (mean age, 34.9 years), before surgery and at 3, 6, and 12 months after surgery. Hormone measurements included LH, FSH, estradiol, testosterone, free testosterone, androstenedione, prolactin, DHEAS, cortisol, growth hormone, and SHBG. These hormone levels were compared with those of 105 healthy men (mean age, 33.9 years).Fourteen of the 22 patients (63.6%) achieved total seizure control following epilepsy surgery. Before surgery these patients' free testosterone and androstenedione concentrations were significantly lower compared with healthy men. In seven of these patients a significant increase of testosterone, free testosterone, and androstenedione levels was observed. Patients without complete seizure control did not show an increase in serum androgen concentrations. The authors concluded that successful temporal lobe epilepsy surgery may lead to a normalization of serum androgen concentrations in men with epilepsy. In a recent study, it was observed that patients with temporal lobe epilepsy were more likely to show abnormal testosterone / luteinizing hormone ratios than patients with extra temporal epilepsy ($p < 0.01$). However, patients receiving AEDs with marked hepatic enzyme-inducing effects were more likely to have low testosterone / luteinizing hormone ratios than patients taking non-enzyme-inducing AEDs or healthy controls ($p < 0.01$). The authors concluded that, both focus localization and AED choice affect male sex hormones (16).

Limitations

The main limitation of this study was the relatively small number of the patients enrolled in the investigation. However, the statistical analysis did not show even a trend in any of the comparisons. Another limitation was absence of healthy control individuals, which was due to financial restrictions. However, this study was a pre- and post-intervention (CBZ treatment) study and absence of healthy controls would not affect the results.

Conclusion

Despite the fact that, sexual dysfunction and reproductive disorders are common among men with epilepsy, the exact pathophysiology of these problems is not clear yet. Most probably, its pathophysiology has a multifactorial nature and sexual dysfunction and reproductive problems in patients with epilepsy has various etiologies. Further studies are required to determine the exact role of epilepsy itself, AEDs, and other possible determinants, such as psychological stress in causing sexual dysfunction and reproductive problems in patients with epilepsy.

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Conflict of interest

The authors have no conflict of interest.

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