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Antiepileptic Drugs, Sexual Functions and Serum Hormonal Profile in Males with Epilepsy

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Abstract

Sexual dysfunctions are a common problem in epileptic men. Etiology is multifactorial involving both epilepsy and antiepileptic drugs. Purpose of this study was to evaluate incidence of sexual dysfunctions in epileptic men, assessing epilepsy, antiepileptic drugs, serum hormonal profile, psychiatric disorders.

Keywords: Sexual dysfunctions; Sex hormones; Epilepsy

Introduction

Sexual dysfunctions significantly reduce the quality of life in general population with a prevalence estimated between 20 and 22%. Most frequent reported sexual dysfunctions are: erectile dysfunction, reduced libido, orgasmic and ejaculation dysfunctions. Aetiology of such disturbances is often related to various co-morbidity such as cardiovascular disease, hyperglycaemia, hypertension and hypercholesterolemia. As far as patients with neurologic disease, epileptic patients are likely to have a greater risk for sexual dysfunctions if compared with general population [1].

Epilepsy is a chronic neurological condition characterised by recurrent epileptic seizures. They happen because of sudden, abnormal electrical activity in the brain, there are many types of seizures and some have mild symptoms. Seizures are divided into two main groups: focal seizures that happen in just one part of the brain, and generalized that are a result of abnormal activity on both sides of the brain. Epilepsy has many possible causes, including illness, brain injury, and abnormal brain development, but sometimes the cause is unknown [2,3].

The epilepsy syndrome and localization influence the presentation of sexual dysfunction. Studies report higher percentages of sexual dysfunction in persons with temporal lobe epilepsy compared to primary generalized epilepsy [4,5]. Not only epilepsy but also Antiepileptic Drugs (AEDs) affect hormones and neuroendocrine systems. So aetiology of such dysfunctions in patients with epilepsy is multifactorial including: disease by itself, epileptic seizures, drug therapy, life style and psychological problems in addition to the physiologic effects of epileptic discharges in brain regions mediating sexual behaviour [6,7].

In patients with epilepsy the prevalence of sexual dysfunctions varies between 38 and 71%; this variability is strictly related to the correct definition of "sexual dysfunction". So, some authors indicate generic sexual dysfunctions with the term "hyposexuality", but more recently, the growing interest in this topic allowed us to identify more exactly the type of sexual dysfunctions: reduced libido, orgasmic and erectile dysfunctions, satisfaction from sexual intercourse and sexual life of the patient [8-10]. The epilepsy itself, type of seizures and their frequency are influencing and influence hypothalamic and pituitary structures and, consequently, the regular hormonal release, inducing an impairment of the correct sexual function [11]. Studies in literature show that temporal lobectomy can reverse hormonal changes associated with temporal lobe epilepsy if complete seizure control is achieved [12,13].

Also antiepileptic therapy, and mainly enzyme-inducing drugs, impaired not only hormonal release, but also the protein- binding sexual hormones, modifying in turn share of active hormone in blood circulation. Furthermore, in people with epilepsy, anxiety, depression and social stigmate are to be kept in mind as they strengthen the illness limiting the quality of life of these patients [14-17].

The aim of the present prospective study is to evaluate the incidence of sexual dysfunctions in males with epilepsy, the type of epilepsy, the frequency of seizures, the type of Antiepileptic Drugs (AEDs) in mono or poly-therapy, the serum hormonal profile and the presence of psychiatric co-morbidity.

Patients and Methods

We enrolled 61 patients, consecutively, focusing on type of epilepsy, frequency of seizures, AEDs, hormonal profile and presence of mood disorders. We excluded all patients with severe neurologic and psychiatric impairment and patient who were not able to fill questionnaires.

Mean age was 31.2 years (range 18-50 years); 31 patients (50.8%) had an idiopathic generalised epilepsy and 30 (49.2%) a focal epilepsy; among them latter 18 (60%) had probably symptomatic type and 12 (40%) symptomatic type (Table 1).

Patients with focal epilepsy included 6 (20%) with frontal lobe epilepsy, 16 (53.3%) with temporal lobe epilepsy, 3 (10%) with occipital lobe epilepsy and 5 (16.7%) with multifocal epilepsy. The seizures were frequent monthly or daily in 29 patients (47.5%).

As far as type of therapy is concerned 48 patients (78.7%) were on monotherapy and the remaining 13 (21.3%) on polytherapy. Valproate (VPA) was the most used drug (25 out of 61 patients; 41%), alone or associated with Carbamazepine (CBZ) (14), Levetiracetam (LEV) and

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Demographics	Cases n= 61 (%)
Mean age	31.2
Focal epilepsy	30/61(49.2)
Generalized epilepsy	31/61 (50.8)
Idiopathic epilepsy	31/61 (50.8)
Probably symptomatic epilepsy	12/30 (40)
Symptomatic epilepsy	18/30 (60)
Frontal lobe epilepsy	6/30 (20)
Temporal lobe epilepsy	16/30 (53.3)
Occipital lobe epilepsy	3/30 (10)
Multifocal epilepsy	5/30 (16.7)

Table 1: Demographics.

Lamotrigine (LTG)(9), Phenobarbital (PB) (8), Topiramate (TPM) (7) and oxcarbazepine (OXC) (6) (Table 2).

All patients enrolled were subjected to measurement of blood total testosterone levels, free testosterone, Dehydroepiandrosterone Sulphate (DHEAS) and delta-4-androstenedione.

Sexual functions were evaluated by means of structural questionnaire "International Inventory of Erectile Function" IIEF which evaluates erectile function (IIEF I), orgasmic function (IIEF II), sexual drive (IIEF III), satisfaction intercourse (IIEF IV) and whole satisfaction of sexual life (IIEF V).

To evaluate mood disorders all patients performed Hamilton Rating Scale for Depression (HRSD). Statistical analysis was performed on the basis of Chi-square test to evaluate categorical variables and Student's t test to analyze continuous variables. Statistical significance level was fixed as $p<0.05$.

The protocol and procedures employed were reviewed and approved by the Local Research Ethics Committee for recruitment patients and the control group.

Results

Out of 61 enrolled patients, 22 (36.7%) showed sexual dysfunctions: erectile dysfunctions in 14 (23%), orgasmic dysfunctions in (11.5%) and sexual drive dysfunctions in 12 (19.7%) (Table 3).

Patients with sexual dysfunctions included 14 on monotherapy and 8 on polytherapy (VPA in 8, 6 PB, 5 TPM, 3 LEV, 3 LTG, 3 OXC).

Out of 61 patients, 36 were subjected to blood measurement of sexual hormones and 21 (58.3%) showed hormonal modifications: blood increased total testosterone was found in 6 patients (16.7%), reduced free testosterone was found in 12 (33.3%) and increased free testosterone in 7 (19.4%). Reduced levels of DHEAS were found in 9 patients (25%) and increased levels of DHEAS associated with reduced levels of Delta androstenedione in only one (Table 4).

In our study, as reported in the literature (Parazzini et al 2000), there is an increased prevalence in sexual dysfunctions (SD), and actually, mean age of epileptics with SD (39.36) is significantly greater if compared with that of patients without SD (29.54) with $t=4.544$ and $p<0.0001$ (Table 5).

There is not any significant association between focal/generalized epilepsy and sexual changes ($\chi^2= 0.132$, $p=0.7167$) nor between focal frontal ($\chi^2= 0.091$, $p=0.7635$), temporal($\chi^2= 0.196$, $p=0.6583$), occipital ($\chi^2= 0.515$, $p=0.4730$), multifocal epilepsy ($\chi^2= 1.297$, $p=0.2547$) and sexual dysfunctions. These latter are not associated with increased frequency of seizures ($\chi^2= 0.309$, $p=0.5783$) (Table 6).

Analyzing data concerning the relationship between sexual dysfunction and AEDs, we did not find any significant association with mono or polytherapy (VPA, LEV, TPM, LTG, CBZ, OXC) ($\chi^2= 3.351$, $p= 0.0672$); except for a weak significance between PB and sexual dysfunctions ($\chi^2= 4.266$, $p= 0.0389$) (Table 7).

Our data do not indicate any association between hormonal changes and focal/generalized epilepsy as well as various types of focal epilepsy (frontal, temporal, occipital, multifocal) (Table 8).

A positive relationship was found between hormonal changes and

On monotherapy	48/61 (78.7)
On polytherapy	13/61 (21.3)
VPA	25/61 (41.0)
LEV	9/61 (14.8)
TPM	7/61 (11.5)
LTG	9/61 (14.8)
CBZ	14/61 (23.0)
OXC	6/61 (9.8)
PB	8/61 (13.1)

Table 2: Drug Therapy.

	Cases n= 61 (%)
Sexual dysfunctions	22/61 (36.7)
Erectile dysfunctions	14/61 (23.0)
Orgasmic dysfunctions	7/61 (11.5)
Sexual drive trouble	12/61 (19.7)

Table 3: Types of sexual dysfunctions.

Hormonal impairment	21/36 (58.3)
Total testosterone increased	6/36 (16.7)
Free testosterone reduced	12/36 (33.3)
Free testosterone increased	7/36 (19.4)
Reduced DHEAS	9/36 (25)
Increased DHEAS	1/36 (2.7)
Reduced Delta androstenedione	1/36 (2.7)

Table 4: Type of hormonal impairment.

	Pts with sexual dysfunctions	Pts with no dysfunctions	t (Student's Test)	p
Mean age	39.36	29.54	4.544	0.0001

Table 5: Mean age of epileptics with sexual changes.

	χ^2	p
Sexual dysfunctions and types (focal or generalized) epilepsy	0.132	0.7167
Sexual dysfunctions and frontal lobe epilepsy	0.091	0.7635
Sexual dysfunctions and temporal lobe epilepsy	0.196	0.6583
Sexual dysfunctions and occipital lobe epilepsy	0.515	0.4730
Sexual dysfunctions and multifocal epilepsy	1.297	0.2547
Sexual dysfunctions and increased frequency of seizures	0.309	0.5783

Table 6: Sexual dysfunctions and epilepsy.

	χ^2	p
Sexual dysfunctions and mono/polytherapy	3.351	0.0672
Sexual dysfunctions and VPA	0.078	0.7795
Sexual dysfunctions and LEV	0.036	0.8485
Sexual dysfunctions and TPM	2.731	0.0984
Sexual dysfunctions and LTG	0.036	0.8485
Sexual dysfunctions and CBZ	2.613	0.1060
Sexual dysfunctions and OXC	0.091	0.7635
Sexual dysfunctions and PB	4.266	0.0389

Table 7: Sexual dysfunctions and AEDs.

	χ^2	p
Hormonal changes and types (focal or generalized) epilepsy	0.214	0.6439
Hormonal changes and frontal lobe epilepsy	0.842	0.3590
Hormonal changes and temporal lobe epilepsy	0.127	0.7219
Hormonal changes and occipital lobe epilepsy	0.968	0.3252
Hormonal changes and multifocal epilepsy	0.029	0.8639

Table 8: Hormonal changes and epilepsy.

the assumption of CBZ but not of other AEDs (VPA, LEV, TPM, LTG, OXC, PB) (χ^2= 5.581, p= 0.0182) (Table 9).

We found, also, an association between hormonal changes and sexual dysfunctions in epileptic patients (χ^2=10.414, p=0.0013), mainly with erectile dysfunction (χ^2=7.659, p=0.0056) and changes of sexual drive (χ^2=4.261, p=0.0390),but not with orgasmic dysfunction (χ^2=0.242, p=0.6228) (Table 10).

Depression and sexual dysfunction are significantly related (χ^2=9.883, p=0.0017): mainly concerning sexual drive (χ^2= 37.773, p<0.0001), and erectile dysfunction (χ^2=5.553, p=0.0185), but not orgasmia dysfunction (χ^2=0.062, p=0.8038) (Table 11).

Discussion

Sexual dysfunctions have been reported in literature in 38.7% of males with epilepsy.

Hyposexuality is the predominant syndrome which is characterized by the loss of sexual desire, reduced sexual activity, and sexual arousal [18,19]. On the other hand organic sexual problems are also frequently seen; for example orgasm disturbances, erectile dysfunction, premature ejaculation and fertility problems due to hypogonadism [20].

In our study we used "International Inventory of Erectile Function" IIEF, a standardized questionnaire, to evaluate different sexual dysfunctions, and we found a prevalence of SD in 36.7% of patients [18,19]. Mean age of epileptics with sexual dysfunctions (31.2 years) is significantly greater if compared with that of patients without sexual dysfunctions, as reported in literature [9]. In nineties Petra et al. pointed out these data, relating them to an increase in levels of Sexual Hormone Binding Globuline (SHBG) in older epileptics [21]. It was hypothesized that ictal discharges involving cortical regions, which mediate sexual behavior, could play a role in genesis of various sexual dysfunctions; in particular limbic region: amygdala, and the corticomedial nucleus (both improving hypothalamic gonadotropin releasing hormone –GnRH - release) [22,23]. It is also possible that epileptic discharges could induce an abnormal bioavailability of serum hormonal concentrations, mainly of testosterone through an influence on hypothalamus, pituitary gland and eventually gonads [24,25].This seems to be confirmed in the study of Bauer et al. when after surgical removal of epileptogenetic focus an increase in serum level of total and free testosterone has been found [26]. Actually several studies showed that particularly men with temporal lobe epilepsy are affected. Temporal Lobe Epilepsy (TLE) is involved assuming an altered secretion of GnRH from the hypothalamus connected to temporal lobe.

In our study we did not find any significant relationship between a particular type of focal or generalized epilepsy and sexual dysfunctions, nor analyzing seizure severity or seizure frequency as it has been described in literature [27]. It could be explain, first of all, considering our small sample.

The reasons for developing sexual dysfunction are multi-factorial. Some of the symptoms are caused by the epilepsy itself while others may be caused by the antiepileptic medication. Analyzing the relationship between AEDs and SD we did not find any significant associations with mono or polytherapy, and the presence of sexual dysfunctions, except for a weak significance between PB and SD. Even if we did not find a statistical significance, it is anyway interesting that we found SD in 8 of 13 patients (62%) on polytherapy, while only 14 of 48 (29%) monotherapy patients were affected. So we may speculate an association between chronic polytherapy and sexual dysfunctions in epileptic men.

As already known in the literature these data could be related to the activity of enzyme-inducing drugs on microsomial system which increase metabolism of sexual hormones, and production of proteins binding sexual hormones (SHBG) actually inducing a decrease of the amount of free, and biologically active, hormone. In a small sample of epileptics who assumed carbamazepine, Connel et al. found a decrease of total testosterone and an increase of SHBG comparing them to a group of controls [27]. Rattya confirmed these results in his study on 90 epileptics who assumed carbamazepine, oxcarbazepine and VPA; only patients who assumed CBZ and OXC showed hormonal variations related to sexual dysfunctions if compared to controls and those who assumed VPA [17,28]. However, there is sufficient evidence to suggest that particularly the strong enzyme-inducing antiepileptic drugs, which are metabolized in the liver, such as carbamazepine, phenytoin, phenobarbital or primidone, change the hormone balance of the male organism. These substances enhance the activity of the hepatic cytochrome-P450 enzyme system and increase the formation of sexual hormone binding globulin which, in return, reduces the free biologically active testosterone and increases the inactive bound form [29]. Because of sexual hormones are very important in supporting sexual drive and sexual function in man and in women it is thought contributing to the sexual dysfunction observed in patients with epilepsy who are on chronic treatments. In our study, due to the small number of patients in each AED group, it would be worth a comparison between SD and AEDS pooling enzyme-inducing versus non-inducing medications. But, because of some patients are on polytherapy, (including both enzyme-inducing and non-inducing AEDs), it couldn't be possible analyzing these data.

Instead we found a statistically significant association between

	χ^2	p
Hormonal changes and VPA	1.150	0.2836
Hormonal changes and LEV	0.166	0.6838
Hormonal changes and TPM	0.242	0.6228
Hormonal changes and LTG	0.823	0.3643
Hormonal changes and CBZ	5.581	0.0182
Hormonal changes and OXC	0.094	0.7598
Hormonal changes and PB	2.222	0.1360

Table 9: Hormonal changes and AEDs.

	χ^2	p
Hormonal changes and sexual dysfunctions	10.414	0.0013
Hormonal changes and erectile dysfunctions	7.659	0.0056
Hormonal changes and sexual drive	4.261	0.0390
Hormonal changes and orgasmic dysfunctions	0.242	0.6228

Table 10: Hormonal changes and sexual dysfunctions.

	χ^2	p
Depression and sexual dysfunctions	9.883	0.0017
Depression and erectile dysfunctions	5.553	0.0185
Depression and sexual drive	37.773	0.0001
Depression and orgasmic dysfunctions	0.062	0.8038

Table 11: Depression and sexual dysfunctions.

the hormonal changes and SD (χ^2=10.414, p=0.0013). In particular an association between blood increased total testosterone, free testosterone and increased levels of DHEAS with erectile dysfunction (χ^2=7.659, p=0.0056) and sexual drive (χ^2=4.261, p=0.0390), but not with orgasmic dysfunction (χ^2=0.242, p=0.6228).

We did not find any significant relationship between a particular type of focal or generalized epilepsy and hormonal changes. Also in our study the presence of hormonal changes does not seem to be associated with any type of AEDs, including the new ones (LEV, TPM, LTG, OXC), except for CBZ (χ^2=5.581, p=0.0182), as reported by Rättyä et al. [17] and Connell et al. [27].

Anyway in epileptic men various mechanisms play a role in sexual dysfunction. Psychosocial factors that can impair sexuality, such as limitation of social contacts and poor self-esteem, affect a relatively large proportion of the population with epilepsy.

In our study we, also, hypothesized that depression could play a role in epileptic males. By mean of HRSD we found a statistically relationship between depression and sexual dysfunctions, mainly concerning change in sexual drive, even though it is not so easy to rule out the possibility that depression is the consequence of sexual dysfunctions.

On the other hand Duncan (2005) also evaluated the association between sexual dysfunctions and hormonal variations indicating a marked decrease in serum values of serotonine as effect of the disease on limbic system within sexual dysfunction. Until now studies relating troubles of mood and sexual dysfunctions are very few, as well as drug therapy

The initial important factor is acknowledgment of sexual dysfunction as a common problem associated with epilepsy. Patients are often too embarrassed to discuss these problems or may even lack subjective appreciation of their presence and extent. Physicians, too, are often uncomfortable about addressing them or may fail to recognize their frequency and importance. For the optimal care of patients with epilepsy, these barriers must be confronted and surmounted.

Conclusion

The results of the present study showed:

- sexual dysfunction are present in 36.7% of enrolled males with epilepsy
- mean age of males with epilepsy is significantly greater than of those without sexual dysfunctions
- there is not any significant association between sexual dysfunctions (focal or generalized epilepsy), as well as with any type of focal (frontal, temporal, occipital, multifocal) epilepsy
- there is any association between sexual dysfunctions various AEDs in the treatment, except for CBZ
- there is not any association between sexual dysfunctions and frequency of seizures
- hormonal changes are associated with sexual dysfunction in males with epilepsy treated with AEDs mainly the erectile dysfunction and change in sexual drive but not with the orgasmic dysfunction
- there is not any association between hormonal changes and type of AEDs, except for CBZ
- depression is associated with sexual dysfunctions, mainly with change of sexual drive and the erectile dysfunction but not orgasmic dysfunction.

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