

## INTERICTAL HYPOSEXUALITY IN MALE PATIENTS WITH EPILEPSY

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**ABSTRACT** - The purpose of this study was to compare the serum levels of androgens between hyposexual and non-hyposexual patients with epilepsy. Adult male patients with epilepsy were investigated. Serum levels of testosterone (T) and free-T, estradiol, and sex hormone binding globulin (SHBG) were measured and the free androgen index (FAI) was calculated. While there were no differences between hyposexual and non-hyposexual patients in the serum levels of T, free-T, and estradiol, or to the FAI, the serum levels of SHBG were significantly higher in hyposexual patients than in non-hyposexual patients. Thus, the effects of increased SHBG upon serum levels of testosterone biologically active in patients with epilepsy and hyposexuality were not detected by the methods used in this study. Four (44%) of nine hyposexual patients who were re-evaluated after two years follow-up improved sexual performance. Thus, clinical treatment that results in good seizure control may improve sexual performance in some patients with epilepsy.

**KEY WORDS:** epilepsy, sexual dysfunction, testosterone, and androgens.

### Hiposssexualidade interictal em homens com epilepsia

**RESUMO** - O objetivo deste estudo foi comparar os níveis séricos de andrógenos e estradiol entre pacientes do sexo masculino com e sem hiposssexualidade. Níveis séricos de testosterona e testosterona porção livre, estradiol e globulina ligadora de hormônio sexual (SHBG) foram dosados e calculado o índice de andrógeno livre (FAI). Não houve diferença significativa de testosterona, porção livre de testosterona, estradiol e de FAI nos pacientes com e sem hiposssexualidade. Os níveis de SHBG foram significativamente maiores nos pacientes hiposssexuais quando comparados com os pacientes sem hiposssexualidade. Deste modo, os efeitos da SHBG aumentada nos níveis séricos de testosterona biologicamente ativa, em pacientes com epilepsia e hiposssexualidade, não foram detectados pelo método usado neste estudo. Quatro (44%) pacientes, reavaliados após dois anos de seguimento, tiveram melhora significativa do desempenho sexual. Portanto, o tratamento medicamentoso, com melhor controle das crises epiléticas, pode melhorar o comportamento sexual de alguns pacientes com epilepsia.

**PALAVRAS-CHAVE:** epilepsia, disfunção sexual, testosterona, andrógenos.

Hyposexuality is one of the most frequent (28%-67%) interictal abnormalities observed in patients with epilepsy<sup>1-5</sup>. Several factors may disrupt normal sexual function in patients with epilepsy, including psychological influences, hormonal disorders, anti-epileptic drugs (AEDs), and the disease itself<sup>6</sup>.

Androgens are important for the maintenance of libido and sexual potency<sup>7,8</sup>. Decreased serum levels of free-testosterone (free-T) have been associated with diminished libido and erectile dysfunction<sup>9</sup>. The majority (98%) of plasma testosterone (T) is linked to proteins, 43% to 45% to albumin, 53% to 55% to sex hormone binding globulin (SHBG), and 2% cir-

culate under free form<sup>10</sup>. The free androgen index (FAI) may indirectly estimate the serum levels of T bound to albumin<sup>11</sup>, which is also considered to be biologically active.

Whether AEDs, the disease itself, or both factors modulate sexual dysfunction in patients with epilepsy remain unclear. While some studies implicate low serum levels of free-T as the cause of hyposexuality<sup>12-16</sup>, other studies<sup>17,18</sup> found normal serum levels of free-T, increased SHBG, and reduced FAI in patients with epilepsy and hyposexuality. The majority of studies investigated sexual function in patients with refractory epilepsy, particularly those can-

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didates to temporal lobe surgical resection. The effects of less severe seizures on sexual function are still unclear.

The purpose of this study was to compare the serum levels of androgens and estradiol between male hyposexual and non-hyposexual outpatients with epilepsy. Patients were inquired about sexual function at the beginning of this study and after two years of follow-up. Clinical variables, including the age of seizure onset, seizure type and frequency, and serum levels of androgens and estradiol were compared among hyposexual and non-hyposexual patients.

## METHOD

### *Subjects*

The Committee of Ethics in Medicine of the General Hospital, Campinas University (São Paulo, Brazil) approved this study. Written informed consent was obtained from both patients and healthy individuals.

Forty-two outpatients from the Epilepsy Unit, Neurology Department, Campinas University, were included during the period of six months. Two patients refused to participate in this study and one patient, who had severe difficulties in relationship with his wife, was excluded. Thus, 39 patients were investigated. Thirty-nine healthy individuals, who used to come with patients to the same hospital, were interviewed about sexual function but not submitted to hormonal dosages. Both patients and controls were selected because of gender (male patients), age (from 20 to 45 years), and marital state (married). In all cases, other associated pathologies, as well as heavy alcohol consumption had been ruled out.

### *Interviews*

Interviews about sexual function were carried out blinded by a second independent investigator. Patients were interviewed at the beginning of this study and after two years of follow-up. The classification of sexual dysfunction was based on Diagnostic and Statistical Manual of Mental Disorders<sup>19</sup>. During the interviews, we followed a routine of anamnesis of sexual function as follows: 1) Libido, including self-report of sexual desire and frequency of search of sexual intercourse; 2) Sexual potency, including frequency of sexual intercourse that culminate in orgasm, frequency of masturbation that culminate in orgasm, capacity to obtain and/or maintain penile erections, approximate duration of penile erections, and frequency of complete erections; 3) Self-report of sexual satisfaction, from completely satisfied to completely unsatisfied with their sexual experiences and performance. Some of the questions about sexual activity were based on Thorne's Sexual Inventory<sup>20</sup>, including the frequency of search for sexual intercourse and the degree of satisfaction in sexual experiences.

Libido was considered decreased or absent when the subject reported diminishment or absence of sexual de-

sire and had frequency of search for sexual intercourse at least less than once a month. Potency and sexual pleasure were considered reduced or absent when the frequency of sexual intercourse that culminate in orgasm were at least less than once a month, and/or when there was a failure persistent or recurrent, partial or complete in obtain and/or maintain penile erections until the end of sexual activity. Sexual satisfaction was investigated in all cases. Those who were satisfied were not considered hyposexual, even with low frequency of sexual activity or decreased sexual desire.

Only the sexual dysfunction that occurred persistently or recurrently during a period longer than six months was considered for analysis. We did not consider temporary or occasional complains about sexual function. In addition, premature ejaculation, which is commonly seen in the general population<sup>21</sup>, was not considered hyposexuality. Those who presented decreased or absent sexual potency and/or libido lasting a period greater than six months and were completely unsatisfied with their sexual experiences were considered hyposexual.

### *Seizure frequency*

The frequency of seizures was divided as follows: a) Very frequent: seizures occurring several times a day or at intervals shorter than seven days; Frequent: seizures at intervals longer than seven days but shorter than 30 days; Occasional: seizures at intervals longer than 30 days but shorter than one year; Rare: seizures at intervals longer than one year.

### *Hormonal dosages*

Blood samples were taken between 9am to 10 am after 30 minutes of rest. Patients were seizure free for at least 48 hours before the blood drawn. The samples were left to coagulate at room temperature, centrifuged, and stored in a freezer at -20°C for further hormonal dosages. Serum levels of T and free-T were determined by radioimmunoassay, serum levels of estradiol and SHBG were determined by immunoradiometric method. The sensitivity of the T-assay was 0.22 ng/ml; the intraassay coefficient of variation was 2.63%; the interassay coefficient of variation was 1.2%. The sensitivity of the free-T-assay was 0.15 pg/ml; the intraassay coefficient of variation was 3.15%; the interassay coefficient of variation was 4.2%. The sensitivity of the SHBG-assay was 0.1 nmol/ml; the intraassay coefficient of variation was 3.58%; the interassay coefficient of variation was 5.1%. The sensitivity of the estradiol-assay was 0.9 pg/ml; the intraassay coefficient of variation was 1.55%; the interassay coefficient of variation was 5.56%. FAI was calculated by multiplying the serum levels of T (nmol/L) by 100 and dividing the serum levels of SHBG (nmol/L) as follows:  $FAI = \frac{TT \times 100}{SHBG}$ .

### *Data analysis*

Thirty-nine patients were selected to participate in this study. For each patient a non-paired control (n = 39) was

selected for comparisons regarding the presence of sexual dysfunction. Subsequently, two groups of patients were compared as follows: a) hyposexual group: patients with epilepsy and sexual dysfunction, b) non-hyposexual group: patients with epilepsy and normal sexual function. It was observed clinical variables related to epilepsy, AEDs, hormonal dosage, and variables related to sexual performance. The Grizzle, Starmer, Koch<sup>22</sup> model was used for comparisons. It was used IBM-PC computer under Windows, with statistical software SAS (SAS Institute, Cary, N.C.). For analysis of sexual interviews, a table of frequency of the conditions before and after was used. Pearson's Q-square was used for tests of independence.

## RESULTS

### *First interview about sexual performance in patients with epilepsy and control group:*

Eleven (28.2%) patients were considered hyposexual. Ten patients had decreased or absent libido and sexual potency and one had decreased sexual potency and unaltered libido. All patients were completely unsatisfied with their sexual experiences and performance. The hyposexuality began after epileptic seizures in all patients. The age of onset of hyposexuality ranged from 26 to 40 years (mean: 32.2). One (2.6%) individual of the control group was considered hyposexual. He had decreased libido and sexual potency. This individual was completely unsatisfied with his sexual experiences and performance. Hyposexuality was more frequently ( $p=0.002$ ;  $\chi^2=9.848$ ) observed in patients with epilepsy than in the control group.

### *Clinical data*

The mean ages of patients with or without sexual dysfunction were identical. Hyposexual patients were between 28 and 45 years old (mean: 35.4) and non-hyposexual patients were between 24 and 44 years old (mean: 35.4). Similarly, no significant differences in education were found between groups. The majority of patients from both groups had not com-

pleted secondary school. All hyposexual (100%) patients and 21 (75%) non-hyposexual patients had partial seizures with or without secondary generalization, and seven (25%) non-hyposexual patients had generalized tonic-clonic seizures. Nine (81.8%) of 11 hyposexual patients and 12 (42.8%) of 28 non-hyposexual patients had temporal lobe epilepsy (TLE; Table 1). TLE was significantly ( $p = 0.028$ ;  $\chi^2 = 4.824$ ) more commonly observed among hyposexual than non-hyposexual patients.

No significant differences were found between groups in relation to the seizure frequency. The frequency of seizures in hyposexual patients was as follows: Four (36.4%) patients had very frequent seizures, one (9.1%) patient had frequent seizures, three (27.3%) patients had occasional seizures, and three (27.3%) patients had rare seizures. The frequency of seizures in non-hyposexual patients was as follows: Seven (25%) patients had very frequent seizures, five (17.8%) patients had frequent seizures, six (21.4%) patients had occasional seizures, and 10 (35.7%) patients had rare seizures. In addition, no evidences of significant differences were found between groups in relation to the age of seizure onset, and type or serum levels of AEDs.

Brain computed tomography (CT) was normal in 29 (74.3%) patients and abnormal in 10 (25.7%) patients. Seven patients with abnormal CT scan fulfilled-up the criteria of possibility for the diagnosis of calcified form of intracerebral neurocysticercosis (23), with multiple or single nodular calcifications. The other three patients had sequelae of head trauma as follows: two hyposexual patients had left frontal and right temporal areas of hypodensity on CT scan, respectively, and one non-hyposexual patient had bilateral frontal areas of hypodensity on CT scan. No significant differences were found between hyposexual and non-hyposexual patients in relation to brain lesions detected by CT scan. Magnetic resonance imaging (MRI) was not performed

Table 1. Mean serum levels of androgens, estradiol, and SHBG, and the mean of free androgen index.

Hormone	Hyposexual	Non-Hyposexual
Total testosterone (T)	7.02 ± 1.17 <sup>o</sup>	6.56 ± 0.45
Free testosterone (free T)	15.44 ± 1.25	14.94 ± 1.11
SHBG	73.97 ± 15.41*	42.78 ± 3.91
Estradiol	16.63 ± 3.68	11.69 ± 1.68
Free androgen index	19.74 ± 2.89	22.8 ± 1.58

<sup>o</sup> Mean ± SEM; \* $p < 0.05$

in all patients in this study and consequently not considered for analysis.

#### *Serum levels of T, FT, SHBG, and FAI (Table 1)*

There was no evidence of significant differences between hyposexual and non-hyposexual patients in relation to serum levels of T, free-T, or estradiol. Similarly, we did not find evidences of significant differences in the FAI between hyposexual and non-hyposexual patients. However, the serum levels of SHBG were significantly ( $p < 0.05$ ) higher between hyposexual than non-hyposexual patients.

#### *Second interview about sexual performance in patients with epilepsy after two-years follow-up period*

Thirty-six (92.3%) patients could be re-evaluated at this time. Among the remaining three patients, two did not return to the routine visits and one developed systemic arterial hypertension and was excluded. Among those patients previously considered hyposexual, nine were re-evaluated. Four (44.4%) had improvement in their sexual performance and were considered non-hyposexual, whereas five (55.6%) continued hyposexual. Among those patients previously considered non-hyposexual, 27 (96.4%) were re-evaluated and one (3.7%) developed hyposexuality. Thus, during the second interview, six (16.7%) patients were considered hyposexual.

All four patients that improved sexual performance during the follow-up period were taking AEDs and had concomitant improvement in seizure frequency as follows: two had no seizures and two had one seizure during the year that preceded the second interview. Among those patients that continued or developed hyposexuality, three had very frequent seizures that were refractory to AEDs treatment and three had occasional seizures. Two of these hyposexual patients with low seizure frequency had sequelae of head trauma in the left frontal and right temporal lobes, respectively.

The analysis of hyposexuality among the first and second interviews about sexual performance was done using table of frequency of conditions before and after. It was used Pearson's Q-square for test of independence. The result ( $p = 0.000$ ;  $\chi^2 = 13.067$ ) shows evidence of significant differences among the first and second evaluations. Although limited by the small sample of hyposexual patients, the results obtained in this study may indicate the benefits of clinical treatment and seizure control on sexual performance in patients with epilepsy.

## **DISCUSSION**

Hyposexuality was more frequently observed among patients with epilepsy than in healthy individuals. We observed hyposexuality in almost 30% of men with epilepsy. The majority of hyposexual patients showed global diminishment of libido and potency. We compared sexual activity before and after two years of follow-up in more than 90% of our patients. The analysis of hyposexuality between the first and second interviews about sexual performance showed evidence of improvement in sexual performance between the first and second evaluations.

Although we did not find any differences between seizure frequency and impairment or improvement of sexual function, our results suggest that some patients with good outcome regarding seizure control improve sexual activity. In this study, 44% of patients that were considered hyposexual improved sexual performance during the two-year follow-up period. In contrast, five patients that persisted hyposexual or developed hyposexuality during the two-year follow-up had either seizures refractory to treatment with AEDs ( $n=3$ ) or sequelae of temporal ( $n=1$ ) or frontal ( $n=1$ ) head trauma. In the former patients, the cause of sexual dysfunction is probably the structural brain lesion in the temporal and frontal lobes, respectively. Previous studies demonstrated that patients with refractory epilepsy improved sexual performance after temporal lobectomy<sup>2,3,5,24</sup>. Based on the fact that both clinical and surgical treatment for epilepsy that result in better seizure control may influence sexual performance, it is possible that the disease itself contributes to hyposexuality.

In agreement with previous studies<sup>1-5</sup>, hyposexuality began after epilepsy in all patients in this study. Temporal lobe seizures were more commonly observed among hyposexual than non-hyposexual patients. Nine (81.8%) of 11 hyposexual patients and 12 (42.8%) of 28 non-hyposexual patients had limbic seizures. Limbic seizures have been associated with hyposexuality in humans<sup>1-5</sup> and animals<sup>25</sup>. In male cats, hyposexuality was observed after amygdaloid seizures but not motor cortex seizures<sup>25</sup>. The temporal lobes have long been involved in the modulation of sexual behavior<sup>26</sup>. In 1939, Kluver and Bucy<sup>26</sup> described hypersexuality, excessive oral tendency, loss of expected fear and anger, visual agnosia, and dietary changes in monkeys submitted to bilateral lobectomy. In humans, post-ictal Kluver Bucy syndrome was observed after temporal lobectomy<sup>27</sup>. Thus, ablation of the temporal lobes exacerbates

sexual activity while human temporal lobe epilepsy usually inhibits sexual function. However, the mechanisms underlying the association between limbic epilepsy and sexual dysfunction remain unclear.

While serum levels of T and free-T were not significantly different among hyposexual and non-hyposexual patients, serum levels of SHBG were increased in the hyposexual group. Previous studies<sup>12,15,17,18,28-30</sup> showed high serum levels of SHBG in patients treated with AEDs. Increased SHBG would expect to produce sexual dysfunction by decreasing serum levels of free-T and/or albumin-bound testosterone, which was indirectly estimated by FAI in this study. However, the effects of increased serum levels of SHBG upon free-T and FAI were not significantly different between groups. Although FAI has been used in several studies, it is controversial whether FAI is an appropriate measurement for males<sup>31,32</sup>. Based on the facts that increased SHBG did not elicit marked differences between hyposexual and non-hyposexual patients in relation to the serum levels of free-T measured by RIA and that FAI may not be reliable for male individuals<sup>31,32</sup>, further study with more accurate measurements of the bioavailable androgens are necessary to elucidate whether increased SHBG contribute to the sexual dysfunction frequently observed in patients with epilepsy.

The serum levels of estradiol did not differ between hyposexual and non-hyposexual patients in this study. The results about serum levels of estradiol in patients with epilepsy and sexual dysfunction are controversial. While Murialdo et al.<sup>33</sup> found increased serum levels of estradiol, Duncan et al.<sup>34</sup> did not find altered levels of estradiol in patients with sexual dysfunction and epilepsy.

Our goal was not to report the complete evaluation for sexual dysfunction in patients with epilepsy. However, all patients in this study were submitted to psychological and urological evaluations. Previously, Souza et al.<sup>35</sup> reported a significant association between sexual dysfunction, anxiety, and depression in male and female patients with epilepsy. Depressive disorders, which are frequently observed in patients with epilepsy<sup>36</sup>, may cause sexual dysfunction. In addition, previous study<sup>37</sup> found vascular impotence in two of 11 male patients with epilepsy and sexual dysfunction. Thus, it is important to empathize that the evaluation of patients with epilepsy and sexual dysfunction requires a multidisciplinary approach.

## CONCLUSION

The results obtained in this study may indicate the benefits of clinical treatment and seizure control on sexual performance in some patients with epilepsy. The serum levels of SHBG were higher in hyposexual than in non-hyposexual patients with epilepsy. However, the effects of increased SHBG on bioavailable androgens, including free-T and albumin-bound T were not detected by the methods used in this study.

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