

SEX HORMONES AND EPILEPSY: NO LONGER JUST FOR WOMEN

Sexual Dysfunctions and Blood Hormonal Profile in Men with Focal Epilepsy. Kuba R, Pohanka M, Zakopcan J, Novotna I, Rektor I. *Epilepsia*. 2006;47:2135–2140. **PURPOSE:** To evaluate the incidence of sexual dysfunction in men with focal epilepsy and to establish their hormonal profiles. **METHODS:** We prospectively analyzed sexual functions and hormone blood levels in 40 male patients (age ranged from 18 to 44 years, with an average age of 27.6 ± 5.6 years) with refractory focal epilepsy. We used the Czech version of the structured questionnaire entitled International Inventory of Erectile Function (IIEF) to assess the patients' sexual functions. The subscales of this questionnaire separately evaluate erectile function (IIEF I), orgasmic function (IIEF II), sexual desire (IIEF III), intercourse satisfaction (IIEF IV), and overall satisfaction with sex life (IIEF V). In all of the patients, the following blood tests were performed: quantitative assessment of blood levels of prolactin (PRL), total testosterone (total-T), free androgen index (FAI), sexual hormone-binding globulin (SHBG), estradiol (E_2), dehydroepiandrosterone sulfate (DHEAS), progesterone (PRG), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). All these quantitative laboratory data were correlated with other clinical variables and with the results of the IIEF. χ^2 and Wilcoxon tests were used for the statistical analysis. A p-value <0.05 was considered to be statistically significant. **RESULTS:** At least one of the types of sexual dysfunction, as defined by IIEF (IIEF I, II, and III), was found in 22 (55%) of the 40 patients (55%). Erectile dysfunction (IIEF I) was found in six (15%) of 40 patients, orgasmic dysfunction (IIEF II) in six (15%) of 40 patients, and loss of sexual desire (IIEF III) in 16 (40%) of 40 patients. According to other subscales of IIEF, 22 (55%) of 40 patients were not satisfied with sexual intercourse (IIEF IV), and 20 (50%) of 40 patients were not satisfied with their sex lives (IIEF V). None of the subscales of IIEF was significantly correlated with the age of the patients or with the duration of epilepsy. In patients with at least one of the sexual dysfunctions (IIEF I, II, and III), we found a statistically significant increase of FSH and SHBG, and a decrease of DHEAS and FAI in comparison with those in the patients with normal sexual functions. In patients with erectile dysfunction, we found the same changes and a significant increase of E_2 . In patients with orgasmic dysfunction, we found a statistically significant decrease of DHEAS. In patients with dysfunction of sexual desire, we noticed a significant increase of SHBG and a decrease of DHEAS and FAI. All patients with orgasmic dysfunction were being treated with carbamazepine (CBZ) in monotherapy or combination therapy. In patients with at least one type of sexual dysfunction (IIEF I, II, and III), we found a higher proportion of valproate treatment in monotherapy or combination therapy in comparison with CBZ. **CONCLUSIONS:** Our study showed a relatively high incidence of sexual dysfunction and dissatisfaction with sexual intercourse and sex life, as defined by the IIEF I–V questionnaire, in men with refractory focal epilepsy. The most frequent dysfunction in these patients is the impairment of sexual desire. However, our study indicates some specific hormonal changes related to various types of sexual dysfunction that are not related to antiepileptic drug treatment.

COMMENTARY

No practicing neurologist can have failed to notice the many journal articles and educational symposia on the effects of epilepsy on women's reproductive health. Catamenial epilepsy, bone health, and effects of seizures and antiepileptic drugs (AEDs) on menstrual cycles, contraception, and pregnancy are familiar topics. In contrast, men's sexual health has been relatively neglected. Fortunately, this research gap appears to be closing, with several recent studies focusing on effects of seizures and AEDs on sexual function, sex hormones, and fertility in men with epilepsy (1–4). In the study, Kuba et al. cross-sectionally assess sexual dysfunction in 40 male patients with refractory focal epilepsy.

Sexual function is a complicated and uncomfortable subject for many physicians and patients. Patients may be reluctant to broach the topic, even when dysfunction is severe. Neurologists rarely are adequately trained to take a thorough sexual history. Once the topic has been raised, assessment may be even more difficult. The etiology of sexual dysfunction in epilepsy is often multifactorial, including structural brain abnormalities, seizures and interictal epileptiform discharges, and AEDs. Psychological factors, such as depression, social stigma, and fear of seizures, may also play important roles. Teasing out the specific etiology in an individual patient can therefore be a daunting task.

The hypothalamic-pituitary-gonadal (HPG) axis regulates gonadal secretion of steroid hormones via a feedback-loop mechanism. Gonadotropin-releasing hormone is released by the hypothalamus and regulates the pulsatile release of gonadotropins (i.e., luteinizing hormone and follicle-stimulating

hormone) from the anterior pituitary, which in turn stimulates the gonads to produce androgens, estradiol, and progestins. In males, luteinizing hormone stimulates Leydig cells to produce testosterone, while follicle-stimulating hormone triggers production of spermatozoa from the Sertoli cells. Inhibin B, androgens, and estradiol provide feedback regulation to the HPG axis.

Both seizures and interictal epileptiform discharges may cause alterations in gonadotropin and prolactin release from the hypothalamus and pituitary, altering sex hormone levels (5). Structural brain abnormalities associated with epilepsy may impact sexual functioning. For example, the amygdala, commonly involved in temporal lobe epilepsy, is an important mediator of sexual function. AEDs play a major role in altering sex hormone levels, both directly, by altering their metabolism and indirectly, by disrupting the HPG axis. Enzyme-inducing AEDs increase the hepatic metabolism of sex hormones and accelerate the synthesis of sex hormone-binding globulin (6). In men, the net result is a decrease in biologically active (unbound and loosely bound) testosterone (3). Enzyme-inducing AEDs also increase the conversion of testosterone to other steroids, such as estradiol (7). Estradiol is an important regulator of the HPG axis, and even small increases can inhibit the normal upregulation response of the axis to low androgen levels (7). Valproate does not change levels of total testosterone (6) but does elevate estradiol levels (8), perhaps by suppressing enzymatic metabolism of estradiol.

Sexual dysfunction is common in men with epilepsy (1–3,7). Estimates of prevalence range from 30 to 70 percent, likely because of differences in patient populations (e.g., partial vs. generalized epilepsy), definitions of sexual dysfunction, seizure frequency, and number and type of AEDs. The recent well-designed studies by Herzog et al., using a 4-item S-score questionnaire to measure sexual interest and potency in men with partial epilepsy, found sexual dysfunction in 20% (2,7). Sexual dysfunction was associated with low androgen levels; among men with low S-scores, 70.6% had bioactive testosterone levels below the control range, compared to 17.6% among men with normal S-scores. Most studies have assessed only older AEDs. Herzog et al. found that patients taking lamotrigine in monotherapy had levels of sexual dysfunction and hormone profiles similar to those of untreated patients with epilepsy and normal controls, but there are no data regarding other new AEDs (2).

This study confirms that sexual dysfunction is very common in men with epilepsy. The authors found at least one type of sexual dysfunction in 55% of the 40 patients, most in the slight or moderate range. The study has several limitations, including small size, cross-sectional design, inclusion of patients taking polytherapy AEDs, and failure to assess potential confounding variables, such as mood. Patients had more severe

epilepsy than in the previously mentioned study by Herzog et al. (2), with seizure frequency ranging from 1 to 15 seizures per month (average 8.4), potentially accounting for the higher likelihood of sexual dysfunction. Likely because of high seizure frequency, most of the patients (83.5%) in the Kuba et al. study were treated with AED polytherapy. Unfortunately, because of the variety of AED combinations, individual AED effects could not be ascertained.

The most novel aspect of this study is the association of hormone abnormalities with different types of sexual dysfunction. The authors utilized the International Index of Erectile Function (IIEF), an assessment tool new to epilepsy studies. The IIEF is a widely used, multidimensional self-report instrument that has been validated in 32 languages (9). The authors therefore were able to ascribe different types of sexual dysfunction to specific hormone abnormalities. Although results need to be confirmed with larger numbers of patients taking monotherapy AEDs, the findings serve to confirm previous reports of the relationship between abnormal hormone levels and sexual dysfunction. The hormone abnormalities described may provide insight into mechanisms and potential treatments for specific types of sexual dysfunction.

Sexual function is a common and important variable in quality of life for patients with epilepsy and should be assessed in all patients. Use of AEDs that do not induce hepatic enzymes may decrease the likelihood of sexual dysfunction, but this outcome has been demonstrated so far only for lamotrigine. The true prevalence of sexual dysfunction in men with epilepsy remains uncertain. Only men with stable sexual partners for 3 months were evaluated in this study, thus excluding the unknown proportion of men in whom sexual dysfunction was severe enough to preclude stable sexual relationships. Men in this study were also relatively young (ages 18 to 44 years). Because bioactive testosterone decreases with age more rapidly in men with epilepsy than in those without (2), older men may be at even higher risk for sexual dysfunction. Patients with mood disorders or those taking serotonin reuptake inhibitors for treatment of depression are at additional risk for sexual dysfunction.

Patients with sexual complaints should be referred for evaluation and treatment, although optimal treatment is not clear. Because the IIEF can distinguish among different types of sexual dysfunction, it would be an excellent outcome tool for a clinical trial of treatment of sexual dysfunction in men with epilepsy. Testosterone replacement therapy and aromatase inhibitors can potentially improve sexual function, but carry a risk of prostate cancer (10). Efficacy will need to be established to justify the long-term risks of such therapies, particularly in young men with epilepsy.

by Susan Herman, MD

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