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How predictable is the erectile function of patients with epilepsy?

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ABSTRACT

Introduction: Erectile dysfunction (ED) is often reported by patients with epilepsy and may be related to endocrine system abnormalities, side effects of antiepileptic drugs, psychiatric comorbidities, and family or social difficulties.
Aims: This study aimed to identify independent predictor factors for ED in patients with epilepsy.
Main outcome measures: the five-question form of the International Index of Erectile Function (IIEF-5).
Methods: Independent predictive factors for ED evaluated by the IIEF-5 questionnaire in 36 patients (mean age: 39 years) with focal epilepsy (mean: 6 seizures/month) were identified by multiple linear regression analysis.
Results: Eight (21.1%) patients were asymptomatic. Among the symptomatic patients, 11 (28.9%) had mild dysfunction, 10 (26.3%) had moderate dysfunction, and 9 (23.7%) showed severe ED. The multiple linear regression model including family income ($B = 0.005$; $p = 0.05$), education levels in years ($B = 0.54$; $p = 0.03$), depressive symptoms determined by HADS depression subscale ($B = -0.49$; $p = 0.03$), and prolactin levels ($B = -0.45$; $p = 0.07$) showed a moderate association ($r = 0.64$) with the IIEF questionnaire and explained 41% ($r^2 = 0.41$) of its variation.
Conclusions: Erectile dysfunction is highly prevalent in patients with focal epilepsies. Education, depressive symptoms, and prolactin levels can predict erectile dysfunction in up to 41% of patients with epilepsy. This preliminary report justifies further efforts to make a large sample size study to identify independent biomarkers and therapeutic targets for ED treatment in patients with epilepsy.

1. Introduction

Epilepsy is a worldwide neurological disease characterized by recurrent epileptic seizures that may affect different physical, emotional, and social aspects of human life [1]. Reproductive and endocrine system disorders were associated with epilepsy as early as 1950 [2], and the prevalence of reproductive endocrine disorders and sexual dysfunction is significantly higher in males with epilepsy than in the general population [3–7]. The mechanisms related to reproductive and endocrine changes in male patients with epilepsy are still not completely understood, but abnormalities in central nervous system control, peripheral hormone levels, or antiepileptic drugs (AEDs) are influencing factors [5,8]. Erectile function is an important indicator of male sexual function. Erectile dysfunction (ED) is defined as a persistent or recurrent partial or complete failure to obtain or maintain penile erection until the end of sexual activity [9], and it has been estimated to occur in up to 65% of men with epilepsy [6,7,10,11].

Prognostic models are statistical models that combine two or more variables of patient data to predict a diagnosis or clinical outcome. Multivariate analyses are particularly useful to control for the several sources of potential confounding bias associated with a variable of interest [12–15]. Such analyses can i) identify variables that are independently associated with a clinical outcome of interest; ii) determine how much the presence of an independent variable can explain the variation of the variable of interest; iii) improve the diagnosis of combined tests or clinical information; and iv) identify possible therapeutic targets for diseases or their symptoms.

2. Aims

We used these techniques to investigate the prevalence of erectile dysfunction in a Brazilian sample of patients with epilepsy, as well as

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the social, demographic, clinical, psychiatric, neuroradiological, and hormonal factors independently associated with this physiological and emotional health indicator in men.

3. Methods

For this cross-sectional study, we interviewed 38 consecutive male patients at the epilepsy clinic of Hospital Governador Celso Ramos and University Hospital of Universidade Federal de Santa Catarina between March 2013 and November 2014. Both hospitals are integrated with the referral system for epilepsy in the state of Santa Catarina in southern Brazil. All patients were followed by the same board-certified clinical neurophysiologist team (KL, RW, and LS), who made the epilepsy diagnosis according to the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) [16]. There were 560 patients followed in our clinic when the study was performed, and 265 of them were male. Male patients were asked to participate in a study to evaluate their endocrine system, including hormonal level measurements. Patients were recruited consecutively until we completed the number of laboratory tests that were made possible by the study financial support. A specific appointment was done to make the clinical evaluation and blood collection for the laboratory tests.

All patients had a routine electroencephalogram recording. Seizure types were clinically classified according to the standards for epidemiologic studies and surveillance of epilepsy by the ILAE Commission on Epidemiology [17]. High-resolution brain magnetic resonance imaging (MRI at 1.5 T) was done in 80% of the patients, and the remaining cases underwent cranial computed tomography (CT). The epilepsy-related variables were retrospectively collected from the medical records by the board-certified clinical neurophysiologists (KL, LSC, and RW) and revised by the principal investigator (RW). The variables related to erectile function, anxiety and depression symptoms, and hormonal and endocrine evaluation were collected prospectively by one researcher (FCFV) following the approved research protocol.

The blood samples of all patients were collected between 8 and 10 a.m. The hormonal levels were determined as previously described [13]. In summary, 5 mL of peripheral venous blood was collected and centrifuged, and the plasma was examined using an Immulite analyzer (Diagnostic Products Corporation — DPC, Los Angeles, CA). A specific Immulite® kit was used for each hormone dosage: FSH (normal range: 0.7 to 11.1 mIU/mL), LH (normal range: 0.8 to 7.6 mIU/mL), prolactin (normal range: 2.5 to 17 ng/mL), estradiol (normal range: ≤56 pg/mL), progesterone (normal range: 0.11 to 0.54 ng/mL), SHBG (normal range: 13 to 71 nmol/L), total testosterone (normal range: >300 ng/dL), and free testosterone (normal range: >6.5 ng/dL). Free testosterone was calculated from the dosages of TT, SHBG, and albumin with Vermeulen's formula [18] through the website http://www.issam.ch/freetesto.htm.

This study was approved by the ethics committees for human research of both hospitals (protocols: HU764.492 and HGCR 2013/0019-1), and informed consent was obtained from all patients.

4. Main outcome measures

The anxiety and depression symptoms were evaluated by using the Hospital Anxiety and Depression Scale (HADS), which is designed to measure psychological distress in nonpsychiatric inpatient populations [19] and has been validated for Brazilian patients with epilepsy [20]. This widely used scale consists of 14 multiple choice items split across anxiety and depression subscales (with even items for each one). The items are rated on a 4-point Likert scale from 0 to 3, resulting in final scores ranging from 0 to 21 for depression and anxiety that can be analyzed separately.

Erectile function was evaluated using the five-item questionnaire from the International Index of Erectile Function (IIEF) [21], which has been validated for Brazilian Portuguese [5,11,22]. The IIEF has been useful for evaluating the sexual function of patients with cardiovascular and metabolic diseases [23], psychiatric disorders [24], and epilepsy [5–7,22]. A score of ≥22 corresponded to an absence of ED, whereas scores of 17–21, 8–16, and 1–7 corresponded to mild, moderate, and severe ED, respectively. The questionnaire was answered by the patients in a private room.

5. Statistical analysis

A univariate analysis was done to determine the association among the social, demographical, clinical, psychiatric (HADS scales), and hormonal variable levels and the IIFE scores (dependent variable). These analyses were done using a Student "t"-test, ANOVA, linear regression, and chi square or Fisher's exact tests. We did multiple linear regression analyses to identify the independent variables associated with the IIEF scores. In these analyses, categorical variables were classified as 0 or 1 if they were dichotomous, and 0, 1, or 2 for variables divided into three categories. The variables were included in the model based on the biological and clinical plausibility and by the bidirectional "*forward*" and "*backward*" criteria. The magnitude of association between each variable and the IIEF was determined by the B coefficient. Values of $p \leq 0.05$ were considered significant. Variable associations with p-values lower than .10 were considered relevant for the model if they had clinical and biological plausibility. The statistical analysis was done using SPSS 17.0 software.

6. Results

Table 1 shows the distributions of the social, demographic, clinical, radiological, and hormonal variables, as well as their associations with the IIEF scores. All patients had focal epilepsies with or without secondary generalization. Patients had at least one seizure with impaired consciousness per year, and a mean of 6 seizures per month. The mean age was 39 years old, with 8 years of education and 21 years of disease duration. According to the IIEF scores, eight (21.1%) patients had normal erectile function. Among the patients with symptomatic disease, 11 (28.9%) had mild ED, 10 (26.3%) had moderate ED, and the remaining 9 (23.7%) had severe ED.

The univariate analyses are shown in Table 1. There was a significant association ($p < 0.05$) between the IIEF scores and education level (years of schooling) and monthly household income. There was a nonsignificant trend ($p < 0.20$) for the association between the IIEF and the age at epilepsy onset; monthly frequency of seizures; HADS scale depressive symptoms; and estradiol, prolactin, and free testosterone levels.

The final model of multiple linear regression analysis that better explains the variation in the IIEF scores is presented in Table 2. The education level ($B = 0.54$, $p = 0.03$) and the household income ($p = 0.005$, $p = 0.05$) were positive and independently associated with the IIEF scores. The depressive symptoms measured by HADS ($B = -0.49$, $p = 0.03$) were negative and independently associated with the IIEF. The prolactin levels showed a trend for a negative association with the erectile function evaluated by the IIEF scores ($B = -0.45$, $p = 0.07$). The regression model including education level, household income, HADS scores for depressive symptoms, and prolactin levels showed a moderate association with the IIEF ($r = 0.64$, $p < 0.0001$). These variables explained up to 41% of the erectile function evaluated by the IIEF questionnaire ($r^2 = 0.41$). All the remaining investigated variables were not associated with the IEEF scores.

7. Discussion

We found an elevated high prevalence (79%) of ED in this sample of young patients with uncontrolled focal epilepsy. An elevated prevalence of ED (50–66%) was reported almost one decade ago by Herzog et al. in American patients [10] and also recently in Brazilian patients with epilepsy (65.1%) [5]. Among the 7.3% of the 55 controls who had ED in