Seizure 25 (2015) 40–48

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Evaluation of penile vascular status in men with epilepsy with erectile dysfunction

Sherifa A. Hamed [a,*], Bruce P. Hermann [b], Ehab M.M. Moussa [c], Ahmad H. Youssef [a], Tarek A. Rageh [a], Yaser E. Elserogy [a], Eman NasrEldin [d]

[a] Department of Neurology and Psychiatry, Assiut University Hospital, Assiut, Egypt
[b] Department of Neurology, University of Wisconsin, USA
[c] Department of Radiology, Assiut University Hospital, Assiut, Egypt
[d] Department of Clinical Pathology, Assiut University Hospital, Assiut, Egypt

ARTICLE INFO

Article history:
Received 15 May 2014
Received in revised form 1 December 2014
Accepted 3 December 2014

Keywords:
Epilepsy
Antiepileptic drugs
Erectile dysfunction
Penile blood flow
Vascular risks

ABSTRACT

Purpose: Erectile dysfunction (ED) is common in males with epilepsy, likely of multifactorial etiology, including possible systemic vascular comorbidities and medication effects. Here we examined male patients for the possibility of a vasculogenic element of ED.
Methods: Research participants included 47 men with epilepsy (mean age = 30.98 years; duration of illness = 13.98 years) and 25 healthy matched men (mean age = 30.36). Erectile function was assessed using the International Index of Erectile Function Questionnaire (IIEF-5). Penile blood flow was assessed using Duplex Ultrasonography (PDU) after intracavernous alprostadil injection. Penile peak systolic velocity (PSV), end-diastolic velocity (EDV) and resistance index (RI) were the functional parameters analyzed. Carotid artery intima media thickness (CA-IMT) was also measured.
Results: Thirteen of the 47 men with epilepsy (23.40% versus 0% for controls) reported ED, and of these patients, 11 (84.62%) had abnormal PDU [PSV = 28.23 ± 6.1 cm/s, $P = 0.0001$; EDV = 2.22 ± 5.71 cm/s, $P = 0.004$; RI = 0.89 ± 0.22, $P = 0.071$] suggesting vasculogic ED. Penile arterial insufficiency was identified in 5 (45.45%), while 6 (54.54%) had mixed arterial insufficiency and venous leak. Compared to patients with high PSV, patients with low PSV had lower IIED-5 scores, higher EDV, lower RI, higher diastolic blood pressure and higher CA-IMT values. There were no differences in depression, anxiety or concentrations of sex hormones. Significant correlations were evident between PDU variables and duration of illness, depression and anxiety scores and CA-IMT values. In multivariate analysis, the association between PDU parameters and CA-IMT values remained significant even after adjustment for other confounding variables.
Conclusions: Vasculogenic ED is frequent with epilepsy and its relationship to systemic atherosclerosis cannot be excluded.

1. Introduction

Epilepsy is a major public health problem.[1] In the general population, the prevalence of epilepsy is estimated to be 8.2/1000, the prevalence even higher in developing countries (10–12.9/1000) (e.g., Colombia, Ecuador, Egypt India, Nigeria, United Republic of Tanzania and Venezuela).[2,3] Abnormalities in sexual function are common comorbid conditions in patients with epilepsy with a nearly five-fold increased risk compared to the general population.[4] Erectile dysfunction (ED), defined as a persistent or recurrent partial or complete failure to obtain and/or maintain penile erection until the end of sexual activity, has been estimated to occur in 50–66% of men with epilepsy.[5] The etiology of ED in men with epilepsy is likely multifactorial, including several categories of risk factors: (a) neuro-endocrinological factors due to abnormalities in the hypothalamic–pituitary–adrenal axis and sex steroid hormones potentially caused by epileptic discharges, particularly of temprolimbic origin,[6–8] (b)

Abbreviations: ED, erectile dysfunction; AEDs, antiepileptic drugs; IIEF-5, International Index of Erectile Function -5 item version; PDU, Penile Duplex Ultrasonography; PSV, peak systolic velocity; EDV, end-diastolic velocity; RI, resistance index; CA-IMT, carotid artery intima media thickness; BDI-II, Beck Depression Inventory (2nd edition); HAM-A, Hamilton Anxiety Rating Scale; SHBG, sex hormone binding globulin.

* Corresponding author at: Department of Neurology and Psychiatry, Hospital of Neurology and Psychiatry, Assiut University Hospital, PO Box 71516, Assiut, Egypt. Tel.: +20 1115324560; fax: +20 88 2333327/2278.
E-mail address: hamed_sherifa@yahoo.com (S.A. Hamed).

http://dx.doi.org/10.1016/j.seizure.2014.12.002
1059-1311/

iatrogenic factors due to the adverse metabolic effects of antiepileptic drugs (AEDs), particularly enzyme-inducing AEDs (EI-AEDs) [i.e. carbamazepine (CBZ), phenytoin (PHT) and phenobarbital (PB)],[9–11] (c) psychosocial factors including depression and anxiety,[12–17] and (d) vasculogenic considerations due to vascular risk factors or atherosclerotic changes associated with epilepsy.[18–32] Vascular comorbidities with epilepsy are not uncommon. However, the possibility of vasculogenic ED with epilepsy is very understudied but may represent a significant consideration due to the fact that chronic epilepsy and its long-term treatment, particularly with EI-AEDs, has been found to be associated with adverse vascular profiles including increased levels of von Willbrand factor (vWF), fibrinogen and oxidized low density lipoprotein (Ox-LDL),[26] hypercholesterolemia/dyslipidemia,[19,24,27] increases in various lipid fractions such as lipoprotein(a) (Lpa),[19] hyperhomocysteinemia (HHcy),[20,22,23,26,32] hyperuricemia,[22] hyperinsulinemia and insulin resistance,[27,28] hyperleptinemia and leptin resistance,[27,28] weight gain and metabolic syndrome.[21,25,26,31] Chronic epilepsy has also been found to be associated with significantly increased carotid artery intima-media thickness (CA-IMT),[23,26,30] higher rates of early death from ischemic heart disease[18] and cerebrovascular stroke,[31] and (e) a combination of these etiologies.

In general, a normal full erection is defined as an erection to more than 90° that is firm to palpation. It is achieved within 15 min and lasts longer than 15 min. Normal erection involves relaxation of the smooth musculature of the cavernous tissue and penile arteriolar and arterial walls resulting in: (a) an increase in the blood flow in both diastolic and systolic phases due to arteriolar and arterial wall dilatation, and (b) venous compression due to trapping of the incoming blood by the expanding sinusoids and compression of the subtunical venular plexuses between the tunica albuginea and the peripheral sinusoids. These reduce the venous outflow and stretch the tunica to its capacity which encloses the emissary veins between the inner circular and the outer longitudinal layers with further decrease in the venous outflow to a minimum. These changes increase the intracavernous pressure (maintained at around 100 mm Hg) and raise the penis from the dependent position to the erect state (the full-erection phase). A further increase in pressure to several hundred millimeters of mercury results in contraction of the ischiocavernosus muscles and this produces the rigid-erection phase.[5]

The hemodynamic of erection in normal and disease states can be determined using Penile Duplex Ultrasonography (PDU). PDU has been widely used to determine and document the presence of penile arterial insufficiency, inflow or outflow types of ED, venous leak, signs of atherosclerosis and scarring or calcification of erectile tissue, in order to predict the response of ED to medications. Various parameters, such as the diameter of the cavernosal artery, peak systolic flow velocity (PSV) and the degree of arterial dilatation and acceleration time, have been suggested for the diagnosis of arteriogenic ED, while end-diastolic flow velocity (EDV) and resistance index (RI) have been suggested for the diagnosis of venous leak. RI is estimated by subtracting PSV from EDV and divided by PSV.[5,33]

PDU can be used to assess penile blood flow in men with epilepsy. PDU spectral wave analysis during full erection obtained after intracavernous injection of vasoactive substance (e.g. prostaglandin E1, or PGE1) has been considered to be the more accurate, most reliable and least invasive evidence-based diagnostic test for the evaluation of penile arterial insufficiency.[33] Previous studies have confirmed the sensitivity of PDU in the detection of arterial insufficiency in patients with various medical vascular diseases and those with risk factors for vascular diseases.[33–35] In the Mayo Clinic series, PDU examination with PSV less than 25 cm/s was found to have a sensitivity of 100% and a specificity of 95% for the diagnosis of severe systemic arterial disease in the same patients implicating the potentially important role of atherosclerosis.[35]

In this investigation we hypothesized that ED in men with epilepsy may have a vascular etiology. To our knowledge, no previous studies have directly investigated the presence of vasculogenic ED in men with epilepsy. PDU was used to assess the status of penile blood flow. We also measured the intima-media thickness of the carotid (CA-IMT) arteries using Duplex Ultrasonography, a sensitive method for detection of early cerebral and systemic atherosclerosis.[36] Patients with normal and abnormal penile arterial blood flow findings were compared in relation to scores of erectile function; demographic-, clinical-, hormonal- and vascular-related risk variables including CA-IMT. The relationship between CA-IMT values and PDU variables was also determined.

2. Materials and methods

We approached 100 adult men with epilepsy to participate in this study and 47 ultimately agreed to undergo PDU examination. Participating subjects ranged in age between 20 and 48 years and duration of illness ranged from 3 to 35 years. Seizure types were diagnosed according to the International League Against Epilepsy (ILAE) criteria.[37] Patients were recruited from the out-patient epilepsy clinic of the Department of Neurology and Psychiatry of Assiut University Hospital, Assiut, Egypt (over a period of one year). All patients were compliant with treatment with conventional AEDs [CBZ or VPA monotherapies or polytherapy (CBZ + VPA)] for at least 6 months before participation in the study. Twenty-five healthy men matched for age- (range: 20–48 years; mean: 30.36 ± 7.59), educational level and socioeconomic status were also included for comparisons. Control subjects were chosen from the patients' healthy relatives who agreed to undergo PDU exam.

Excluded were subjects (patients and controls) with any of the following: (1) history of neurological disorder other than epilepsy likely to affect erectile function, (2) concomitantly known vascular risk or manifest atherosclerotic vascular disease [e.g. heavy smoking, diabetes mellitus (DM), hypertension (HTN), hypercholesterolemia/dyslipidemia, hyperuricemia, coronary artery disease (CHD) such as angina pectoris or myocardial infarction (MI)], heart failure, cerebrovascular stroke or transient ischemic attacks (TIAs), (3) history of systemic illness unrelated to vascular disease likely to affect erectile function (e.g. renal failure, serum creatinine concentration >150 mmol/l, chronic hepatic illness), (4) history of clinically significant genitourinary disease, pelvic trauma, pelvic surgery, or radiation therapy, (5) alcoholism or diagnosed substance abuse and/or previous hospitalization for substance abuse, (6) use of any regular medication(s) in addition to AEDs (e.g. antihypertensive drugs, heart medications, antidepressants, tranquilizers, and sedatives), and (7) current or recent treatment of ED with intracorporeal injection or application of vasoactive drugs.

The study protocol was approved by the Ethical Committee of the Faculty of Medicine of Assiut University, Assiut, Egypt and all patients and control subjects gave their informed consents to participate in this study.

All patients and healthy subjects underwent the same research protocol, which included the procedures described below.

2.1. Medical, neurological, endocrinological, psychiatric, vascular and urological histories and examinations

Seizure variables included age at onset, precipitating factors, duration of illness, seizure type, seizure frequency, family history of epilepsy, AED(s) (monotherapy or polytherapy), duration of treatment, degree of seizure control on AED(s) and side effects of medications. Seizure frequency was defined as[24]: (a) very frequent: