



Sexual problems in males with epilepsy— An interdisciplinary challenge!

Eva Hellmis*

Kometenplatz 29, 47179 Duisburg, Germany

KEYWORDS

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Summary Sexual function can be altered in patients with different types of epileptic disorder, especially those with temporal lobe epilepsy. The awareness of sexual function disturbances, giving an enormous impact on someone's quality of life, should lead to therapeutic measures. The incidence, evaluation and therapeutic options are demonstrated and seen through the urologist's eyes.

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Introduction

Disturbances in sexuality signify a major limitation in quality of life and may have harmful effects on nearly all areas of life in those affected by these conditions, which is a very important indicator of the patients health status.^{1,2} Epidemiological studies showed that the overall prevalence of erectile dysfunction in men in the general population worldwide is approximately 20–22%, which means that sexual problems have much more impact on public health status than usually assumed.^{3–6}

The leading sexual function disorders in men include reduction of libido, erectile dysfunction as well as orgasm and ejaculation disorders. In more than 60% of men who complain about erectile dysfunction organic reasons, especially endothelial and metabolic dysfunction like hypertension, coronary heart disease, hypercholesterolemia and diabetes mellitus^{3,2,6} underlie the symptoms. In men, some age-related disorders for example benign prostate

hypertrophy and the so-called LUTS (lower urinary tract symptoms) are frequently accompanied by erectile dysfunction and the necessary operative therapy will by itself lead to sexual dysfunction in 4–10% of the patients.^{6,7}

Other reasons for developing sexual dysfunction are age, life-style, alcohol- and nicotine-abuse, obesity and drug-induced side effects⁶. It is often discussed, but not well studied yet how deep the impact of therapeutic necessary drug intake is on sexual function in detail.

It was clearly demonstrated that patients with different types of neurological disorders have a higher risk to develop sexual dysfunction than the general population.

About 40 million people are affected with epilepsy worldwide^{8,9} and numerous symptoms of sexual disorders can be seen in patients with epilepsy. Sexual activity itself can provoke a seizure through hyperventilation and triggering the genital sensory cortical area. Sexual phenomena may also be a part of an epileptic seizure, for example motor symptoms such as erection, ejaculation, orgasm, pelvic sexual movements, or compulsive masturbation.¹⁰

* Tel.: +49 203493142; fax: +49 203495467.

E-mail address: eva.hellmis@gmx.de.

Up to 60% of the male patients with epilepsy are affected by sexual function disorders. Hyposexuality is the predominant syndrome which is characterized by the loss of sexual desire, reduced sexual activity, and inhibited sexual arousal.^{9,11} On the other hand organic sexual problems are also frequently seen. Especially a lack of spontaneous nocturnal and morning penile tumescence, orgasm disturbances, erectile dysfunction, premature ejaculation and fertility problems due to hypogonadism and hyperprolactinemia with consecutively reduced sperm quality.^{11,12}

Studies showed that due to sexual problems, male patients have a lower marriage rate and have fewer children than expected.¹³

A correlation between hyposexuality and the seizure severity or seizure frequency has been described. It has been shown that longer periods of remission are associated with lower rates of hyposexuality. Recently published studies show that the risk of manifested sexual dysfunction is increased with poor seizure control and also with depression, which is a common comorbid disorder in epilepsy.^{14–16} This leads to the suggestion that adequate treatment – invasive operative methods or modern medical treatment – of epilepsy may lead to an improvement of sexual function.^{5,15,17,18}

It has not yet been shown clearly if the onset of epilepsy and/or a remission prior the age of 12–14 are correlated with a better sexual performance. Gastaut and Collomb postulated in 1954, that the onset of seizures prior or during puberty may have a strong effect on the hypothalamic–pituitary axis decreasing the gonadotropin levels with consecutive effects on the sexual performance and behaviour, but recent studies could not confirm this.^{17,19}

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.^{12,20,21} Several studies showed that particularly men with temporal lobe epilepsy are affected.

Epileptiform discharges from the temporal lobe region may be transmitted through amygdala–hypothalamic pathways, disrupting the normal pulsatile secretion of gonadotropic hormones and the basal levels of dopamine secretion, resulting in hypogonadism and hyperprolactinemia that leads to hyposexuality, lack of libido, erectile dysfunction and reduced sperm quality.^{4,18–20}

However, there is sufficient evidence to suggest that particularly the strong enzyme-inducing antiepileptic drugs, which are metabolised in the liver, such as carbamazepine, phenytoin, phenobarbital or primidone, change the hormone balance of the male organism. These substances enhance the activ-

ity 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. This is thought to contribute to the sexual dysfunction observed in patients with epilepsy who are on chronic treatments.^{19,22}

With modern antiepileptic drugs that exert no or only a marginal effect on the cytochrome-P450 enzyme system of the liver, this phenomenon is more or less negligible.

This fact should be taken into account when administering antiepileptic medication to men—especially if therapy is started in adolescent or juvenile men.^{16,18,23}

Evaluation

The initial evaluation of any patient with sexual, especially erectile dysfunction, should be done with awareness for the multi-factorial etiologies. It is not plausible to consider anticonvulsant medication as the only cause of sexual dysfunction in men with epilepsy. Besides the epilepsy itself, the prescribed antiepileptic drugs and psychosocial components, other organic and medication-induced factors might be causative. Interdisciplinary diagnostic strategies are necessary.

The initial evaluation of patients with sexual dysfunction should therefore include a full endocrine and metabolic status. Serum levels of testosterone, estradiol and prolactin, and the thyroidal function should be evaluated. The correction of free testosterone level is the easiest way to regain sexual desire and fertility disorders.

Erectile dysfunction can be the first clinical sign of an unknown and untreated coronary heart disease, so it is important to be informed about concomitant diseases, especially the cardiac condition of the patient. Furthermore, unforeseen drug–drug interactions between the established and the planned drugs for sexual therapy can be minimized when the patient is well investigated and his general practitioner is involved.

The medication history plays an important role. Beside the antiepileptic therapy, there are many possible drug side effects leading to sexual dysfunction, for example β -inhibiting agents, sedatives, antidepressants and diuretics.

The clinical investigation should include the urogenital region, the size of the prostate and the emptying mechanism of the bladder. There is some evidence that treatment of bladderneck obstruction and lower urinary tract symptoms (i.e. with alfuzosin retard, anticholinergic agents) may lead to bet-

ter sexual performance. The IIEF-score (international index for erectile function) and the erection hardness score helps to standardize erectile dysfunction and are useful and clinical instruments to show success during therapy.^{2,24} The nocturnal tumescence measurement is useful, but needs hospitalisation over night to get correct results and is a diagnostic tool that plays a minor role in the diagnosis and therapy of outpatients. It helps to distinguish between organic and psychogenic erectile dysfunction: physiological erectile dysfunction should impair daytime and nocturnal erections equally.

Furthermore a psychological screening for depression and anxiety disorders and a complete evaluation of his sexual and relationship history is necessary to understand a patient's complaints. Life stressors should be considered as contributing factors to sexual disturbances.

Therapy

Once the etiology of sexual dysfunction is determined, proper treatment strategies should follow. The sequential procedure should be first to treat the epilepsy and then, if the neuroendocrine dysfunction of the patient persists, to discuss a supplemental hormonal therapy.

Modern antiepileptic treatment should – besides seizure freedom – also include the challenge of achieving the best conditions for sexuality and fertility for the treated patient. Several studies demonstrate that there is a remarkable benefit for patients suffering from hyposexuality using or switching to antiepileptic agents with no or less enzyme-inducing effect. Thus, oxcarbazepine may be a more effective form of treatment in patients with epilepsy suffering from hyposexuality.²³

If the erectile dysfunction is physiologically mediated, additional pharmacologic treatment may be necessary. The first-line therapy is erection-enhancing phosphodiesterase type-5 inhibitor drugs (sildenafil, vardenafil, tadalafil). These drugs are safe and highly effective, but will not have any impact on sexual desire and interest. So patient education and follow-up appointments are essential to ensure optimal outcomes of pharmacological treatments for sexual dysfunction. For example McCollough et al. could show that treating erectile dysfunction with sildenafil needs up to eight times use of the drug to achieve the best clinical result.^{25–27}

Due to the metabolism of sildenafil by the cytochrome-P450 liver-enzyme system a dose-adaption for the PDE-5-inhibitors might be needed especially

if the patient's antiepileptic treatment is based on enzyme-inducing agents (carbamazepine, valproate, phenytoin).

There are a few case reports^{28,29} of tonic-clonic seizures following the use of PDE-5 inhibitors (2 cases with sildenafil, 1 case with vardenafil). All the patients had no pre-existing lesion and no previous seizure-events in their history. The suggestion is that the epileptogenic potential of the drug itself may be causative or the seizure was provoked by its vascular complications.²⁹

Further therapy options for sexual function disorders belong to the urologist's armamentarium: placing an elastic constricting band at the base of the penis to prevent outflow of blood, using a vacuum device and creating negative pressure drawing blood into the cavernous body to achieve and maintain erection. More invasive regimens, but well effective are the intraurethral application of prostaglandin E1, so-called MUSE, or the intracavernosal self-injection of papaverine, phentolamine and prostaglandine E1 (SKAT). The urologists nowadays prefer the prostaglandine E1-agents to avoid the risk of unwanted prolonged and painful erection (priapism).^{27,30}

Surgical treatment, for example the implantation of a hydraulic penis-prosthesis may be used effectively in individual cases, when the therapy-strategies mentioned above failed.

Often underestimated but nevertheless one of the most important success factors of a therapy of sexual disorders is the involvement of the patient's partner. An expert counselling is helpful, and above all there is a need of minimizing impairing co-factors (metabolic disturbances, obesity, lifestyle, nicotine-abuse).

Still today, the therapeutic options for the treatment of ejaculation and orgasm disorders are not sufficient. The premature ejaculation, focus of ongoing studies, is the next problem that will hopefully be solved with help of short-time selective serotonin reuptake inhibitors that can be used in clinical practice very soon. The therapeutic options accessible today are non-approved, but more or less effective: topical application of local anaesthetics (gel, spray, cream containing lidocaine or prilocaine), manual pressure on sexual trigger points, oral intake of clomipramine and SSRI-agents like fluoxetine, paroxetine and sertaline. The suggestion is that SSRI drugs lead to desensitization of 5-hydroxytryptamine receptors retarding the ejaculation reflex. In animal studies it was demonstrated clearly that activation of the 5-HTA1 receptors facilitates ejaculation. It is assumed that in men these receptors have similar effects, but evidence-based data about their role in men is still lacking. Adverse

effects include fatigue, mild nausea especially if taken on an empty stomach, loose stool or perspiration. Patients may also report diminished sexual desire and weak erections. It may be necessary to combine SSRI and PDE-5-inhibitors to handle these effects.³¹

Conclusion

Sexual dysfunctions are genuine, common, relevant, distressing and complicated human bio-psycho-social conditions. Men with epilepsy have been found to have an increased risk of erectile dysfunction in up to 57%. The management of sexual disorder must include interdisciplinary investigational and therapeutic strategies. Besides, an internist's evaluation, a cardiologic and a urogenital evaluation should be done because of comorbidities and their impact on sexual performance. Hormonal disturbances have to be corrected to regain sexual desire and potency. The antiepileptic medication can not be considered as the only reason for sexual dysfunction in men with epilepsy, but there is a need of avoiding long-time intake of enzyme-inducing agents due to the consecutive hypogonadism and hyperprolactinemia with erectile and fertility problems. Further scientific efforts should be made to find out more clearly how prominent the role of antiepileptic medication is in developing of sexual dysfunction compared to the impact of the epilepsy itself.

When treating epilepsy, one has to consider that in addition to achieving seizure freedom, one must pay attention to sexuality, quality of life and the patient's partnership as well. The urologic therapeutic options for sexual dysfunction in males with epilepsy concentrate on enhancing and maintaining erection. The use of PDE-5 inhibitors seems to be safe and effective in men with neurological disorders, but is not yet well investigated in men with epilepsy which should be the focus of further studies. Finally, therapy of sexual disorders is more than prescribing a pill or giving testosterone, it is based on communication.

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