



Erectile dysfunction in patients with neurologic disorders

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ABSTRACT - Erectile dysfunction (ED) is a common problem in patients with neurological disorders, although frequently overlooked and insufficiently managed. It is usually caused by lesion of the nervous system, but it can also be psychogenic or drug-induced. Various psychological disorders and social or environmental factors play an important role as well. Approximately one third of adult men in Europe have ED and the prevalence is significantly higher in patients with neurological disorders when compared with normal population. According to various studies, the prevalence of ED ranges from 37.5% in patients with Parkinson's disease to up to 75% in patients with multiple sclerosis. Treatment options include oral administration of phosphodiesterase 5 inhibitors alone or in combination with behavioral therapy and psychotherapy. Due to its major impact on the quality of life, it is necessary to promote awareness and diagnosing of sexual dysfunction in everyday clinical practice.

Key words: erectile dysfunction, neurologic diseases, phosphodiesterase-5 inhibitors

INTRODUCTION

Erectile dysfunction (ED) is a common problem in patients with neurological disorders, although frequently overlooked and insufficiently managed. Usually, it is caused by lesion of the nervous system, but it can be drug-induced. Various psychological disorders and social/environmental factors play an important role as well. Epidemiological studies conducted in Croatia, although limited by sample size and sampling methods, confirm the findings of an increased incidence and prevalence obtained by similar studies in other countries. As expected, the prevalence of ED is significantly

higher in patients with neurological disorders when compared with normal population (1).

Sexual dysfunction in men includes decreased libido, ED (lack of spontaneous or nocturnal erections, the inability to achieve an erection) and ejaculation disorders (decreased satisfaction after ejaculation, premature ejaculation, retrograde ejaculation, decreased volume of ejaculate). The avail-

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ability of pharmacological treatment highlights the importance of early recognition of ED in everyday neurological practice, while libido and ejaculation disorders are mainly (though not exclusively) in the focus of experts working in andrological, urological and psychiatric departments.

Erection is a hormonally and emotionally controlled neurovascular phenomenon (2). The physiological mechanisms that lead to ED include complex sensory, neurological and psychological stimuli. The process of achieving penile erection involves the integration of psychological, neurological, and vascular processes, which combine to initiate a physiologic response within the penile vasculature. Endothelial mediated dilation of arteriolar smooth muscle results in increased blood flow into the sinusoids of the corpora cavernosa and subsequent filling while simultaneously relaxing to increase compliance. This filling obstructs venous outflow from the penis by compression of the veins against the tunica albuginea, resulting in penile erection (2). According to the definition of the American National Institutes of Health (NIH), ED is the inability to achieve and maintain an erection sufficient for satisfactory intercourse (3). Occasional ED occurs in virtually all men of different ages, but to be referred as pathological, they should be present for months and have gradual deterioration.

Data on the incidence of ED in Croatia, especially in groups of patients with increased risk are lacking, due to the insufficient number of high-quality epidemiological studies. The possible discomfort (in patients or health providers) when dealing with ED can impede proper diagnosis and treatment. The aim of this article is to promote the awareness of ED in order to avoid neglecting of sexual dysfunction in everyday clinical practice having in front a patient with neurological disorders, such as stroke, Parkinson's disease (PD), multiple sclerosis (MS) and epilepsy, especially when efficient therapy is becoming easily available.

EPIDEMIOLOGY

Erectile dysfunction affects approximately 40 million men in the European Union, and it is predicted that this number will be doubled in 2025 (4). It is believed that more than 50% of men aged 40-70 regularly or occasionally suffer from ED (4). Results of the Massachusetts Male Aging (MMA) study, the largest study of sexual dysfunction to date, have shown that 10% of all men suffer from a

severe form of ED, 25% have moderate and 17% mild disability (4). Prevalence rates ranged from 40% at the age of 40, to 67% of men aged 70 years and older. The incidence rate of erectile dysfunction was 26% in MMA study (5), 65.6% in a study performed in Brazil (6), and 19.2% in a study performed in The Netherlands (7). If these results are applied to the Croatian population, where it is estimated that the number of men aged 40-70 years is more than 840,000, the number of patients with ED would be around 280,000.

Today, it is considered that 70%-80% of all ED cases are caused by organic dysfunction, i.e. endothelial dysfunction and atherosclerosis in the first place, followed by complications of diabetes, prostate surgery (prostatectomy), other endocrine diseases, injuries, structural abnormalities, side effects of medications (antihypertensives, antidepressants, antipsychotics, antihistamines, etc.) (4,8,9). Drugs of abuse can also induce ED (alcohol, amphetamines, narcotics, cannabis, and cocaine). In contrast to organic ED, psychogenic ED is a result of the negative attitude due to inappropriate sexual education, partner pressure, troubled family environment, anxiety, stress, fear of failure, difficulty in controlling the situation, etc. Neurological patients may, therefore, develop ED as a result of organic lesions, but also due to psychogenic result of their illness.

PATHOPHYSIOLOGY

Normal erection can be compromised by dysfunction of one or more of the following functions: mental health, hormonal functions, central and peripheral nervous system, and blood flow to the penis. Basically, normal erection depends on complex interaction of neural, vascular, psychological and endocrine mechanisms.

Depending on the neural mechanisms involved, we can talk about three subgroups of erection: psychogenic, reflex, and so-called non-sexual nocturnal erections. Each subgroup includes three stages: the initial trigger/stimulation, achieving, and maintaining penile erection. Psychogenic erection occurs under the influence of neural impulses whose origins can be either in the central or in the peripheral nervous system. The initial trigger can be visual, auditory, or fictitious stimulus. The stimulus is transferred to the center located in the spinal cord at the level of Th11 to L2 ('the thoracolumbar erection center'). From there, impulses continue to travel to the target organ, i.e. vascular

network of spongy erectile bodies (corpora cavernosa and spongiosa) of the male reproductive organ. The nerve endings in the endothelial cells of the erectile bodies excrete nitric oxide (NO) necessary for the synthesis of cyclic guanosine monophosphate (cGMP), which acts as a vasodilator by relaxing smooth muscles in the blood vessels of the erectile bodies. Relaxation of blood vessels increases blood flow to the penis and consequently an erection occurs. The phosphodiesterase 5 (PDE-5) enzyme breaks down cGMP, leading to cavernous muscle contraction and termination erection.

Reflex erections are achieved by tactile stimulus applied to the penis or genital area that stimulates reflex arc with center located at the sacral spinal cord levels S2-4 ('sacral erectile center'). Young men are more likely experiencing psychogenic, unlike older men whose ED is predominantly of reflex nature.

Non-sexual or nocturnal erections usually occur three to four times during the night, and are first experienced in the adolescent period. They may go unnoticed, even though most of nocturnal erections are present at awakening and usually disappear after bladder emptying. Nocturnal erections occur only during REM sleep. Men with depression, sleep interruption, and abnormal/reduced REM phase do not have nocturnal and early morning erections.

Recent studies identified age as the most prominent risk factor for development of ED. In addition, it was found that ED shares the same risk factors with cardiovascular disease (lack of physical activity, high blood pressure, obesity, smoking, high blood cholesterol levels) (10). There was a strong link between the symptoms of ED and coronary disease (11). It was also found that smoking doubles the risk of ED (12).

ERECTILE DYSFUNCTION IN NEUROLOGICAL PATIENTS

Stroke

The risk factors for ED overlap with the risk factors for cardiovascular and cerebrovascular disease, such as age, smoking, obesity, diabetes, hypertension, dyslipidemia, drug abuse, and the presence of cardiovascular disease as an independent risk factor (10-12). On the other hand, ED is a powerful predictor of cardiovascular death and other cardiovascular complications in patients at high risk,

where it occurs as a result of advanced atherosclerosis and endothelial dysfunction (13).

Although rarely documented, ED is a common symptom in patients with a history of stroke, having a significant impact on the patient's quality of life. In a study by Reese *et al.*, 104 patients with stroke were clinically monitored for 10 months and 54 of them developed ED (14). The parameters that were analyzed were age, marital status, previous diseases, vascular risk factors, etiology of stroke, and score on the modified Rankin scale and NIHHS scale. The results showed that the incidence of ED after stroke was 51.92%. ED developed with an average latency of 5 months after cerebrovascular accident, and showed a tendency to progress in 70.4% of patients. Hypercholesterolemia was found to be an independent risk factor for predicting ED occurrence and severity. ED was moderate in 61.1% of patients and well tolerated in almost half of the respondents. Although there is no evidence that sex increases the risk of stroke, almost 50% of patients were afraid of stroke recidivism and avoided sexual relations (15). In addition, the presence of motor deficit decreases sexual desire and leads to ED, and it may even contribute to the development of accompanying depression (16). Organic brain damage, especially in the area of the hypothalamus, may cause ED. Finally, ED may be a side effect of certain medications, such as antidepressants and antihypertensives (beta-blockers), which are often used in patients with a history of stroke (17).

Multiple sclerosis

Erectile dysfunction is extremely common in patients with MS. When considering the young age of patients with MS, the impact of ED on the quality of life is indisputable (18). Approximately 50%-75% of patients with MS have sexual dysfunction (19). Demyelinating lesions in the spinal cord are the most common cause of ED (20,21), but fatigue, spasticity, loss of sphincter control, pain, development of depression, loss of self-confidence, anger and anxiety contribute to the development of ED as well. An epidemiological study performed in Taiwan compared 38,139 patients with ED and 262,848 individuals without ED. Conditional logistic regression analysis showed that the incidence of MS was 2.23 times higher in the group of ED patients than in the group without ED as a control group (20). The results were adjusted according to several factors such as hypertension, diabetes, coronary heart disease, hyperlipidemia, overweight,

alcohol dependence, and even monthly income and geographic location.

Epilepsy

Connection between epilepsy and ED has long been known. In a study conducted on 6,427 patients with ED and 32,135 healthy controls, logistic regression analysis showed a hazard ratio for previously diagnosed epilepsy of 2.13 for generalized epilepsy and 1.64 for partial epilepsy (22-24). The results were adjusted according to several factors such as hypertension, diabetes, hyperlipidemia, kidney disease, heart disease, obesity, alcohol dependence and socioeconomic status. The strongest correlation was found in the population aged between 30 and 39 years (hazard ratio for previous diagnosis of epilepsy 3.04). A decrease in sexual desire and potency was observed in 14%-66% of patients with epilepsy. Some studies have shown a higher incidence of ED in complex partial epilepsy than in generalized epilepsy. Again, great impact of the social and psychological factors was observed as well (22-24). Various antiepileptic drugs such as phenytoin, carbamazepine and valproic acid can modulate hormonal balance by affecting the hypothalamo-pituitary-gonadal axis, thus directly influencing sexual behavior. New-generation antiepileptic drugs seem to be safer in preserving normal sexual function (25).

Parkinson's disease

Non-motor symptoms are an integral part of PD and often precede motor symptoms. ED is the most common problem in the spectrum of sexual dysfunction. The prevalence of ED among patients with PD is 60%, in comparison with the prevalence of 37.5% in the age-matched controls (26,27). Dopamine replacement therapy can ameliorate ED, thus highlighting the role of dopamine in desire, erection and sexuality. In some patients, dopamine in therapeutic doses can cause hypersexuality. If applying PDE-5 inhibitors in patients with Parkinson's disease, one must have in mind their possible hypotensive effect. Deep brain stimulation of subthalamic nucleus can recover sexual function in patients with PD (28).

The pathophysiological mechanism of ED in patients with PD is still unknown. One study found reduction of testosterone in PD patients, and according to another study, the autonomic nervous system dysfunction was a major cause of ED (29). In the treatment of ED among patients with PD,

sildenafil and apomorphine are often used, although their efficacy is lower than in healthy individuals, probably due to slow bowel motility.

DIAGNOSIS OF ERECTILE DYSFUNCTION

Identifying organic or psychogenic cause of ED is the major diagnostic challenge. Evaluation of ED starts with a detailed medical history. Metz and Seifert have shown that most patients expect their physicians to examine their sexual dysfunction (30). In contrast to widespread perception that sexuality is unimportant in older age, several studies have shown that individuals find the possibility of maintaining sexual relationships an important component of their quality of life (31). If the patient confirms the existence of ED, medical history should include questions about past illnesses and risk factors that can cause ED. Patients need to be asked about the existence of psychogenic, reflex and nocturnal erections, as well as their sexual habits and expectations. The diagnosis of ED is facilitated by the use of standardized questionnaires such as the IIEF-5, which is shown in Table 1 (32).

Standard neurological examination can be expanded by testing cremaster reflex and reflex of anal sphincter, when there are features supporting injury of the lumbosacral spine (L1, S2-S5). Due to multifarious causes such as neurological, urological and psychological, approach to patients with ED is multidisciplinary and requires simultaneous cooperation of more specialists (neurologist/neurophysiologist, urologist, endocrinologist, cardiologist, psychiatrist, etc.). Such an approach is generally reserved for those patients who do not have clear cause of ED, for those in whom ED is the first symptom of the disease, or for those who do not respond to standard therapy. For erection testing, one of the PDE-5 inhibitors (sildenafil, tadalafil) or expensive papaverine and prostaglandin-E1 (PGE-1) can be used. Ten to fifteen minutes after intracavernous application, erection occurs in patients with normal erectile function or psychogenic erectile dysfunction.

TREATMENT OF ERECTILE DYSFUNCTION

In the last two decades, basic and clinical research has led to the development of new therapeutic options in the treatment of ED. The introduction of

Table 1. *The International Index of Erectile Function (IIEF-5) Questionnaire*

Over the past 6 months:					
1) How do you rate your confidence that you could get and keep an erection?	Very low 1	Low 2	Moderate 3	High 4	Very high 5
2) When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5
3) During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5
4) During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5) When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5

IIEF-5 scoring:

The IIEF-5 score is the sum of the ordinal responses to the 5 items.

22-25: No erectile dysfunction

17-21: Mild erectile dysfunction

12-16: Mild to moderate erectile dysfunction

8-11: Moderate erectile dysfunction

5-7: Severe erectile dysfunction

oral preparations in the treatment was a major breakthrough. Today, the treatment of ED is effective. As ED represents a symptom, not a disease *per se*, treatment of the underlying condition is obligatory as first line treatment. Complete resolution of ED can be expected in cases of psychogenic ED and in treatable hormonal disorders such as hypogonadism or hyperprolactinemia. According to the European Association of Urology – European Association of Urologists) (EAU), treatment options include behavioral therapy, oral drug therapy, and use of devices for vacuum erection (33).

Behavioral therapy represents a change in lifestyle with avoiding risk factors such as smoking, alcohol, etc. The first step is to accept the problem, and if the problem is psychogenic, psychiatric treatment, carried out individually or in pairs, is necessary.

The drugs of first choice in the treatment of ED are PDE-5 inhibitors. During sexual stimulation, the terminals of cavernous nerves release NO. NO causes release of guanylate cyclase, an enzyme that catalyzes the formation of cGMP, which causes va-

sodilation and erection. The PDE-5 enzyme hydrolyzes cGMP in cavernous body of the penis, causing reduction of blood flow and consequently inhibiting the erection. In contrast, PDE-5 inhibitors prevent cGMP breakdown, causing an increase in blood flow to the cavernous bodies and prolonged erection. These drugs are not erection stimulants

Table 2. *Contraindications for use of PDE-5 inhibitors*

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|--|
| A. Use clearly contraindicated |
| 1. Concurrent use of nitrates |
| B. Cardiovascular effects may be potentially hazardous (use dependent of clinical assessment) |
| 1. Patients with active coronary ischemia who are not taking nitrates (positive exercise test for ischemia) |
| 2. Patients with congestive heart failure and borderline low blood pressure and borderline low volume status |
| 3. Patients on a complicated multidrug antihypertensive program |
| 4. Patients taking drugs that can prolong the half-life of PDE-5 inhibitors |

Table 3. Comparison of effects and side effects of PDE-5 inhibitors and apomorphine (modified from Porst, 2006)

Drug name	Doses (mg)	Efficacy after admission (minutes)	Co-administration with nitrates	Absorption	Side effects
Sildenafil	25, 50, 100	30-60	No	Reduced with fatty meals	Headache, facial flushing, blurred vision, rhinitis
Tadalafil	10, 20	Prolonged effect up to 36 hours	No	Not reduced with fatty meals	Headache, dyspepsia, low-back pain, rhinitis, facial flushing
Vardenafil	5, 10, 20	30	No	Reduced with fatty meals	Headache, facial flushing, dyspepsia, rhinitis, low-back pain
Apomorphine	2, 3	20	Yes	Absorption is not related with meals	Rarely

and cannot work alone. For appropriate action, sexual stimulation and anatomical preservation of the cavernous nerve are mandatory.

Currently, there are three PDE-5 inhibitors on the market. Sildenafil is in use since 1998, and shows effectiveness 30-60 minutes after taking. It is recommended in doses of 25, 50 and 100 mg. Its absorption can be slowed down if taken with fatty meals (34,35). Tadalafil is a relatively newer agent that appeared on the market in 2003. It has a prolonged effect, up to 36 hours after ingestion. It can be taken with fatty meals and is recommended in doses of 10 and 20 mg (36). Vardenafil also appeared on the market in 2003. Today, it is considered to be the most potent drug for ED. It is effective 30 minutes after application. If taken with fatty meals, absorption is reduced. It is recommended in doses of 5, 10 and 20 mg. All PDE-5 inhibitors are associated with an increased risk of cardiovascular complications. They can cause hypotension, especially in combination with nitrates and they are absolutely contraindicated in patients with severe cardiovascular disease. Other contraindications for use of PDE-5 inhibitors are severe heart disease, unstable angina pectoris, history of recent ischemic stroke or heart attack, and liver or renal failure. PDE-5 inhibitors should not be given to a male person under the age of 18, and are not intended for use in women. Table 2 shows the contraindications for use of PDE-5 inhibitors (37).

Apomorphine is another agent that should be mentioned. Apomorphine is an agonist of dopamine receptors, which enhances erectile signals in the brain. It is applied sublingually in doses of 2 or 3 mg, and erection occurs after 20 minutes. There are

very few side effects and its effectiveness is not related to diet measures. Apomorphine can be taken concurrently with nitrates. Previously applied as an aphrodisiac, yohimbine is now out of use in the treatment of ED (38). Table 3 shows the most important characteristics of the drugs used for ED (39).

If there is failure of therapeutic effect of pharmacological treatment, and the patient refuses penile prosthesis, application of a device for vacuum erection is a possible option. Although the efficiency is high, still there is a high dropout rate because of heavy handling the device.

The second line treatment is recommended for patients with cavernous nerve damage and those who do not respond to oral medications. The treatment options include intracavernous injections of PGE-1 and drugs that are inserted into the urethra (suppository PGE-1). When applied in the cavernous body of the penis, Alprostadil causes erection by relaxation of smooth muscles of the cavernous bodies. The effect is almost instantaneous. Alprostadil is often used as the test for differentiating psychogenic and organic origin of ED. The application requires education of patients and is characterized by a relatively high dropout rate. Complications include prolonged erections, bleeding, priapism (painful erections) and fibrosis of the cavernous bodies. PGE-1 suppositories have the same mechanism of action, but due to the long time of absorption, the effect is delayed and the effectiveness is slightly lower.

The third line treatment is installation of penile prosthesis in patients lacking benefit of pharmacological treatment, and in those seeking permanent

solution. Prostheses can be semi-rigid and hydraulic. In most patients, triple hydraulic prostheses are installed making erection more natural. After installing the prosthesis, libido and ejaculation are preserved, and sexual activity is achieved after 4-6 weeks. The most common complications are infections and mechanical malfunction (40).

CONCLUSION

Erectile dysfunction is a growing health problem that affects the physical and mental health of the individual and undermines the relation between the partners. It is estimated that one-third of adult men in Europe have ED. Studies have shown that ED may be the first sign of serious cardiovascular disease. In addition, risk factors for the development of ED are almost identical as those for developing cardiovascular diseases (hypercholesterolemia, diabetes mellitus, hypertension, smoking and obesity).

So far, there are no adequate epidemiological studies on ED in Croatia and no real indicators of the extent of the disorder, especially in neurological patients. The most common neurological disorders (stroke, epilepsy, multiple sclerosis and Parkinson's disease) are associated with a higher prevalence of ED. In patients with the above mentioned conditions, ED emerges due to a combination of psychological and organic factors such as organic lesions of the brain and spinal cord, spasticity, incontinence, pain, fatigue, depression and fear of the disease worsening. A significant part of ED that should not be forgotten is drug induced (antidepressants, anticonvulsants, beta-blockers).

Physicians should be aware of the importance of the person's sexuality and presence of ED, especially when there are oral preparations that can significantly improve sexual function. In addition, psychotherapy can significantly contribute to treatment success, especially when having in mind that psychogenic ED can be completely cured. PDE-5 inhibitors have high efficiency with very few side effects and minimal interactions with other drugs, and are considered to be the first treatment option regardless of ED etiology. ED is an integral part of the clinical picture in patients with various neurological conditions, which can be diagnosed and successfully treated. Sexuality investigation should be part of the neurological examination, with due respect of the patient's privacy and integrity.

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Eretilna disfunkcija u bolesnika s neurološkim poremećajima

SAŽETAK - Eretilna disfunkcija u neuroloških bolesnika je značajna, ali u Hrvatskoj nedovoljno dijagnosticirana i liječena, a posljedica je neuroloških lezija, medikamentne terapije, psiholoških poremećaja i socijalnih uvjeta u kojima bolesnik živi. Danas u Europi eretilnu disfunkciju ima 1/3 odraslih muškaraca. Eretilna disfunkcija u neuroloških bolesnika ima veću prevalenciju u odnosu na opću populaciju. Prema različitim istraživanjima kreće se od 37,5 % kod Parkinsonove bolesti do 75 % u bolesnika s multiplom sklerozom. Liječenje se danas uspješno provodi peroralnim pripravcima - inhibitori fosfodiesteraze 5 sami ili u kombinaciji s bihevioralnom terapijom i psihoterapijom. Eretilna disfunkcija je značajni dio kliničke slike neuroloških bolesnika pa je kao dio kliničkog pregleda potrebno promovirati ispitivanje o seksualnim funkcijama.

Ključne riječi: eretilna disfunkcija, neurološke bolesti, inhibitori fosfodiesteraze 5