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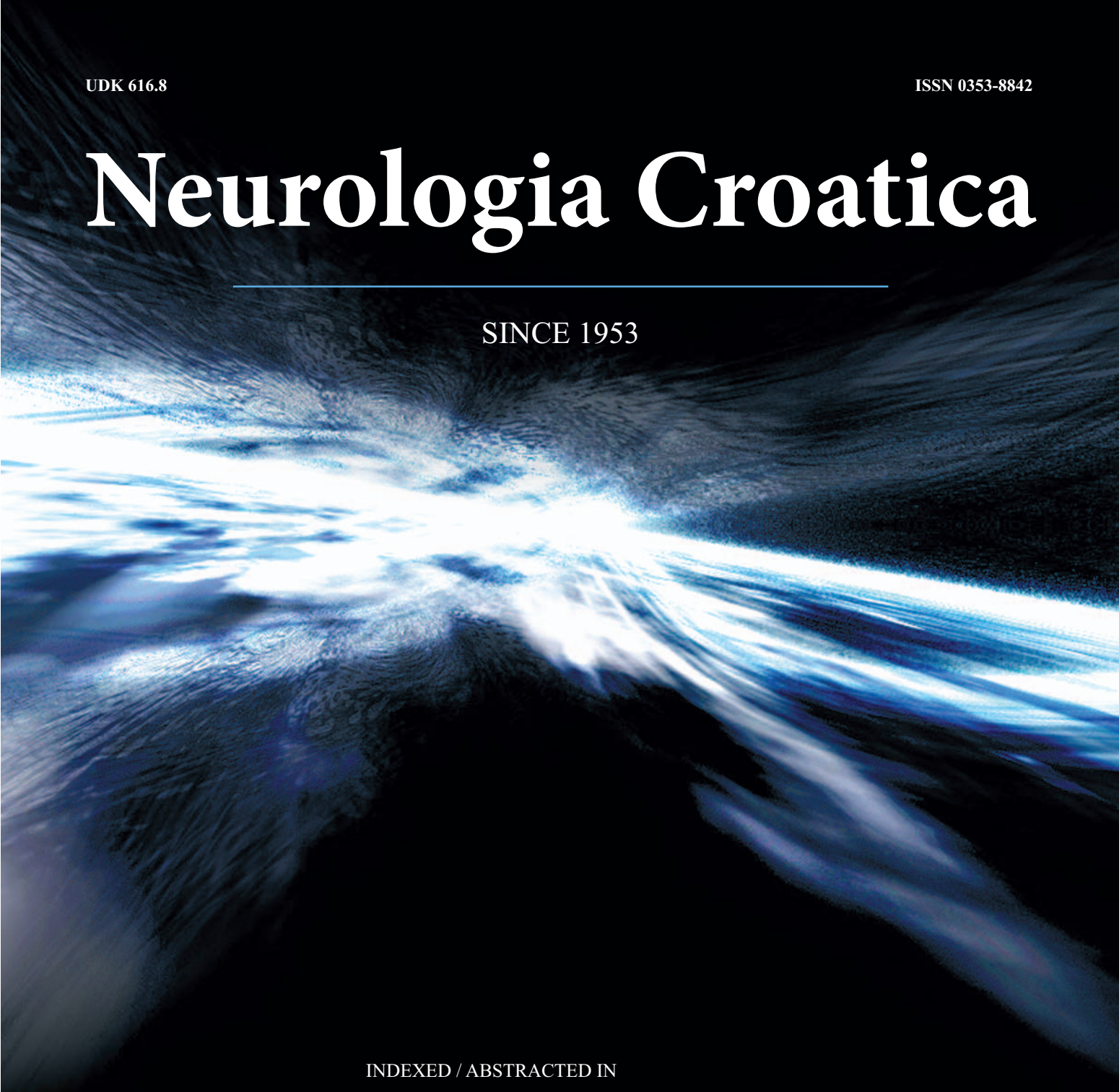

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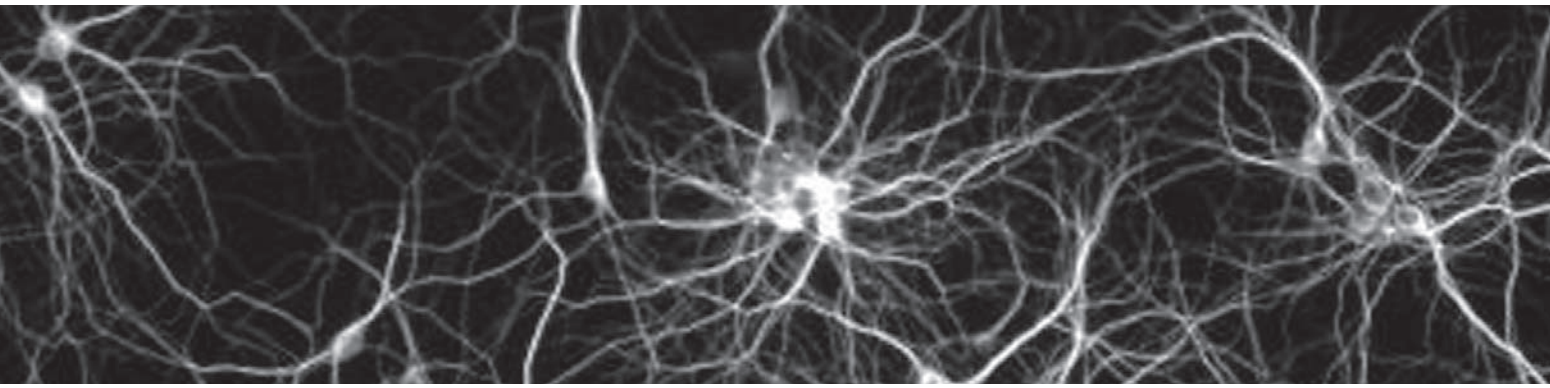
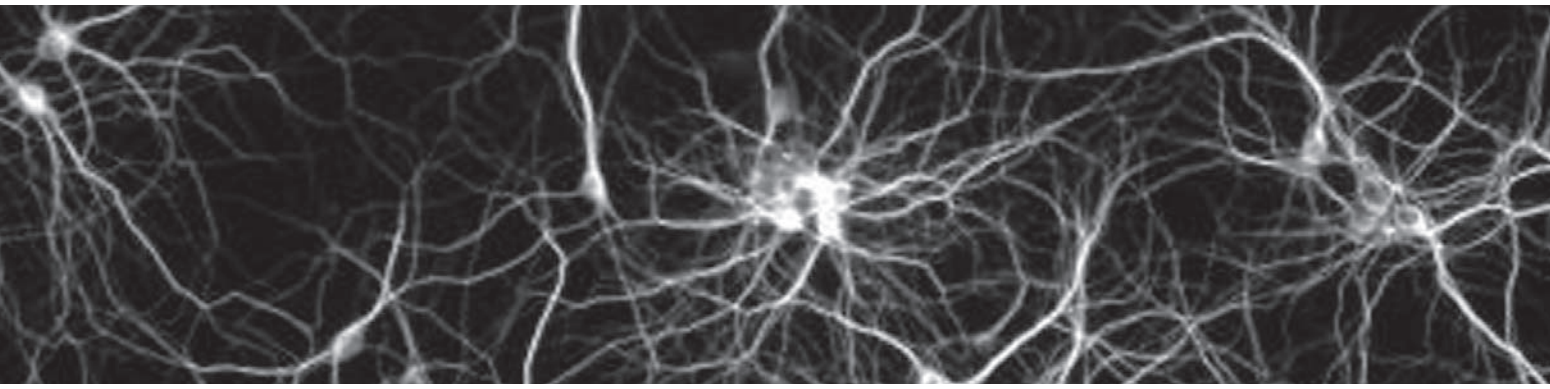


Editorial

Dear reader,

Here is the new issue of the journal *Neurologia Croatica* in its changed edition. Upon the Editorial Board decision, the journal will now appear in English and new sections are included: *Case Records of the Zagreb University Hospital Center* and *Images in Neurology*. This issue is dedicated to the autonomic nervous system through two clinical reports on diagnostic and therapeutic options for neurally mediated syncope and erectile dysfunction in neurologic diseases. In addition, there is a report on conventional MR findings in patients with Creutzfeldt-Jakob disease. The newly introduced sections include reports on self-mutilation in a patient with frontotemporal dementia and on MR findings in spinal cord infarction. Your contributing to the quality of your and our journal by submitting your papers for publication in *Neurologia Croatica* will be highly welcome.

Professor Damir Petravić, MD, PhD
Associate Editor
Neurologia Croatica



Neurally mediated syncope

A. Ljilja[1], A. Mišmaš[2], I. Adamec[2], M. Habek[1,3]

ABSTRACT - Neurally mediated or vasovagal syncope is the most common cause of transient loss of consciousness. Too excessive response to different triggers (emotional stress, scenes of blood, prolonged standing, etc.) results in brief and self-limiting loss of consciousness caused by a sudden drop in blood pressure with or without heart rate drop, which leads to transient brain hypoxia. Prior to the episode of syncope, the patient can have a sensation of nausea, sweating, pallor, and visual field narrowing. Although it is known that in the syncope background there is dysregulation of blood pressure control, the pathophysiology is still unclear. Blood pressure regulation involves complex afferent signals from the aortic arch processed by the central nervous system and efferent modulation of the heart and vascular system. Vasovagal syncope usually does not require treatment. However, in some cases to rule out other causes of fainting, such as arrhythmias, a broad diagnostic work-up is required, for which head-up tilt table test is most commonly used. Frequent vasovagal syncope adversely affects patient's quality of life and pharmacological treatment with β-blockers, such as metoprolol, selective serotonin reuptake inhibitors and vascular constrictors like α-agonists can be administered. Other techniques to reduce hypotension are foot exercise, compressive stockings, increased fluid and salt intake. In more serious cases of vasovagal syncope with bradycardia or asystole, insertion of the electric pacemaker is an option.

Key words: bradycardia, head-up tilt table test, hypotension, neurally mediated syncope

INTRODUCTION

Syncope is a transient loss of consciousness with complete and fast recovery of consciousness and previous neurological functions. In general, it can be classified as vasovagal (situational, neurally mediated), cardiac or orthostatic syncope. Older patients are more prone to orthostatic syncope, carotid sinus hypersensitivity and cardiac syncope, while younger patients are more prone to vasova-

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gal syncope (VVS). Other syndromes with similar presentations are seizures, metabolic and psychogenic disorders, and acute intoxication.

Patients with frequent episodes have greater possibility of severe clinical disorders compared to patients with isolated syncope (1). VVS is a common problem in the population. About 3.5% of people experience one or more episodes of VVS in lifetime (2). Approximately 40% of cases remain undiagnosed, while 30% of patients experience recurrent episodes (3). The pathophysiology of syncope is a complex hemodynamic response with marked hypotension, bradycardia and loss of consciousness. Syncope is caused by baroreflex dysfunction, neuroendocrine response, and inadequate response of the central nervous system to stressor. Episodes of syncope in today's lifestyle can cause discomfort and inconvenience for the patient. In most cases, medical history, physical examination and standard electrocardiogram (ECG) are sufficient for diagnosis (3). Although there are many different therapeutic measures to prevent syncope, its treatment is largely empirical and suboptimal, which is a result of heterogeneous patient population and the lack of controlled randomized trials (4). In most cases, detailed medical history is enough to determine the causes of fainting. The term 'pre-syncope' is used to describe a situation that resembles the prodromes of syncope, but is not followed by loss of consciousness. It is believed that the pathophysiological mechanisms of pre-syncope are the same as in syncope (5).

Epidemiology

Syncope is a common clinical disorder with the annual incidence of 1.3 to 2.7 *per* 1,000 inhabitants (2). Epidemiological studies indicate that approximately 40% of people in the general population have experienced at least one episode of syncope (6). Clinical studies show that the peak incidence of syncope is between 10 and 30 years of age (7). In younger patients, neurally mediated syncope is the most common cause, whereas in older patients cardiovascular causes are more frequent (8).

Etiology and pathophysiology

Physiological regulation of blood pressure consists of the afferent signals processed by the central nervous system, and the efferent modulation of the cardiovascular system (9). Normal regulation of arterial blood pressure is controlled by baroreceptors located in the aortic arch and carotid sinus. Afferent signals are transmitted from the aortic arch *via* vagal nerve and from the carotid sinus *via* glossopharyngeal nerve to the central nervous system. Distension of the vascular structures after cardiac systole results in discharge of afferent nerves that converge from the nucleus tractus solitarius to the brainstem. At this point, efferent sympathetic flow is inhibited and efferent vasovagal flow is increased (10).

The most commonly used model for the neurally mediated syncope is the Bezold-Jarisch reflex in which excessive venous load begins a chain of events that culminate in vasodilatation and bradycardia, which consequently leads to hypotension and loss of consciousness (11).

Excessive venous load of the lower extremities results in decreased ventricular volume, which activates sensory receptors in the inferoposterior wall of the left ventricle, which responds to pressure changes by increasing nerve outflow to the central nervous system *via* vagal nerve. Parasympathetic activity accompanied by vasodilatation and bradycardia increases (12). It is believed that different modulators of the central nervous system activity can cause vasovagal syncope. The potential mediators in the development of vasovagal syncope are serotonin, adenosine and opioids. The β endorphin level is increased in patients during syncope. Different clinical presentations of vasovagal syncope, variable outcome and syncope induced by the tilt-up test with drugs, such as isoproterenol, nitroglycerin and clomipramine indicate that complex pathophysiological mechanisms cause vasovagal reaction.

Neurohumoral theory

Experimental models have shown that the injection of serotonin into cerebral ventricular areas can cause similar sympathetic withdrawal response as in vasovagal syncope (13,14). Selective serotonin reuptake inhibitors (SSRI) can be successful in the treatment of vasovagal syncope (15). Some authors suggest that because the SSRI facilitate nerve transmission, they cause SSRI receptor down-regulation in the brainstem, which results in a blunted response to rapid shifts in the central serotonin levels (15-18).

Dysregulation of cerebral flow

More than 35 years ago, some authors suggested the patients with VVS to have abnormal cerebral vascular response to orthostatic stress, which may

be associated with the pathophysiology of this syndrome (19). This concept is supported by findings on cerebral vasoconstriction and reduced cerebral blood flow in patients with VVS.

CLINICAL PRESENTATION

History data on environmental factors are important for the diagnosis, since syncope is often caused by the sight or loss of blood, sudden stressful or painful experience, surgical manipulation or trauma. Precipitating symptoms and signs are pallor, weakness, yawning, nausea, hyperventilation, blurred vision and impaired hearing immediately before syncope. The patient falls in horizontal position and after a few seconds or minutes returns to consciousness. While regaining consciousness, the patient may experience a feeling of weakness, but usually does not show signs of confusion. VVS is mostly associated with benign prognosis. A small proportion of patients have recurrent attacks of syncope, which can affect their quality of life, mainly due to frequent falls and injuries (20).

Although most patients shows typical signs of VVS such as dizziness and full recovery after a few minutes, up to 30% of patients have an atypical presentation (21).

In case of a longer duration of cerebral hypoperfusion, cramping of body resembling epileptic seizures may occur (22). Patients often report fatigue, weakness, dizziness, sweating, blurred vision, tinnitus and loss of vision. Some patients experience trauma due to the fall, although severe traumatic injuries are rare.

Syncope in children is common. Most episodes are benign and neurally mediated. Only a small portion is potentially life threatening. Diagnosis is primarily achieved by medical history and standard ECG (23).

Patients with frequent syncope have a reduced quality of life, similar to that in patients with severe rheumatoid arthritis or chronic low back pain (24). Patients report difficulties in activities of daily living (71%), driving (60%), physical activity (56%) and walking (42%). Patients with syncope have a high incidence of psychological problems, especially anxiety and depression (25).

Neurally mediated syncope is associated with absenteeism from school in children and from work in adults (26). One retrospective study (27) collected data from medical records on the emotional impact of VVS and expressed stressful aspect. More than half (56%) had a history of mood disorder and 21% were taking psychotropic medications. Psychological problems include suicidal thoughts, depression, panic attacks and chronic anxiety, which is similar to the level of emotional symptoms in chronic patients.

DIAGNOSTIC EVALUATION

Therapeutic and diagnostic guidelines of the European Society of Cardiology define standards for the management of syncope and propose a model of organization for patient evaluation (23). Blood tests, cardiac workup (ECG, echocardiography, holter ECG), head-up tilt table test (HUTT), electroencephalography (EEG), transcranial vessel ultrasound and neuroimaging are diagnostic procedures for syncope. Despite all clinical tests, the cause of syncope remains undetermined in 30% of patients.

HUTT allows for reproduction of syncope and monitoring the patient's physiological responses during syncope. Direct observation and documentation of symptoms during the test give a precise diagnosis and information for treatment and control of the symptoms (28). In patients with cardiac symptoms, echocardiography, stress testing, holter ECG, loop recorder and electrophysiological tests are recommended.

Tests for neurally mediated syncope are HUTT and carotid sinus massage, and in case of negative results, holter ECG and loop recorder. Patients with rare episodes of syncope probably have neurally mediated syncope and diagnostic tests are usually not needed (23).

Clinical characteristics related to the specific causes such as VVS are absence of cardiac disease, long-term history of syncope, provocation by unpleasant event, smell, sound or pain, prolonged standing, crowded, warm environment, nausea and vomiting. Presence of structural heart disease, appearance during exertion, chest pain and sudden death in the family are typical for cardiac syncope. Psychiatric evaluation is recommended when symptoms suggest somatization disorder, or if the patient has a psychiatric disease.

Basic laboratory tests are indicated in cases in which syncope is caused by the loss of circulating volume or in case of metabolic disorders. In patients with suspected heart disease, echocardiography, holter ECG and electrophysiological monitoring are recommended. For patients with chest pain

Table 1. *VASIS classification (34) is used for interpretation of head-up tilt table test*

Type 1 – mixed	Both blood pressure (BP) and heart rate (HR) are reduced. BP reduction precedes HR reduction. HR decreases by >10%, but HR does not decrease to less than 40 beats/min (Fig. 1)
Type 2 – cardioinhibitory	Decrease in both BP and HR, and BP decrease precedes decrease in HR. Type 2A: minimum HR is less than 40 (Fig. 2), type 2B: there is asystole for 3 seconds or more (Fig. 3)
Type 3 – pure vasodepressor	BP is decreased but HR does not decrease more than 10% (Fig. 4)
Chronotropic incompetence	No HR increase in spite of tilt
Excessive HR rise (more than 130 beats/min)	This pattern is associated with postural orthostatic tachycardia (POT)
Positive carotid sinus massage	Test needs to be terminated due to one of the criteria after carotid sinus massage

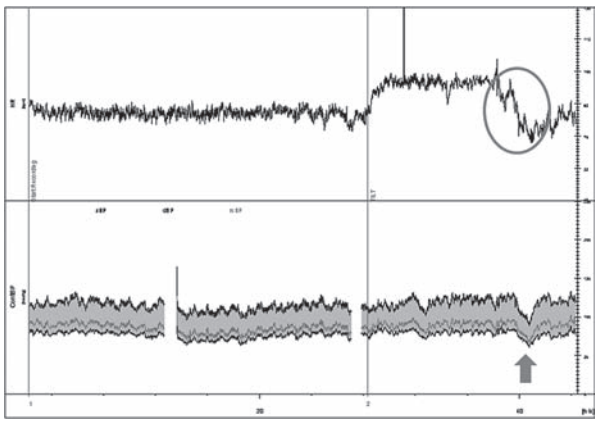

Fig. 1. *Head-up tilt table test in a 22-year-old female patient with a history of recurrent loss of consciousness during vaccination, standing in line and piercing. The circle in the heart rate line shows drop in heart rate and the arrow in blood pressure line shows minimal blood pressure values at the time of syncope.*

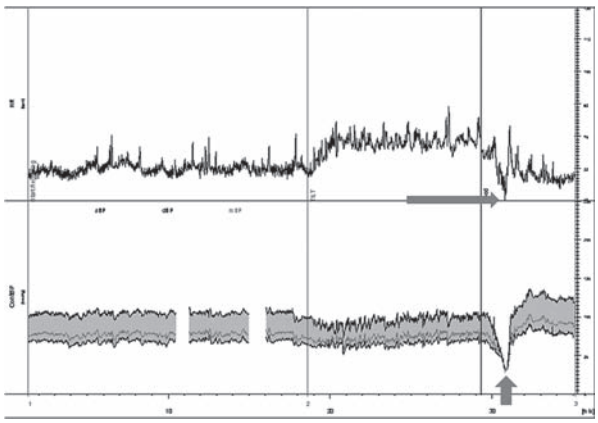

Fig. 3. *Head-up tilt table test in an 18-year-old patient showing asystole (upper arrow) and lowest blood pressure (lower arrow). The patient complained of headache, dizziness and a feeling of confusion at that time.*

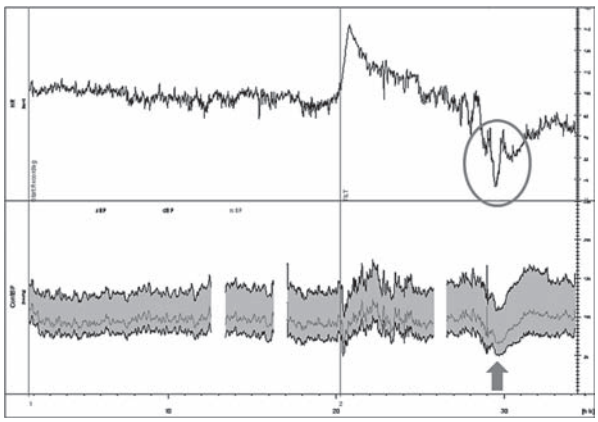

Fig. 2. *Head-up tilt table test in a 45-year-old female patient with recurrent syncope precipitated with pain. In circle: drop of heart beat, frequency less than 40 beats per minute. The arrow shows minimal blood pressure during syncope.*

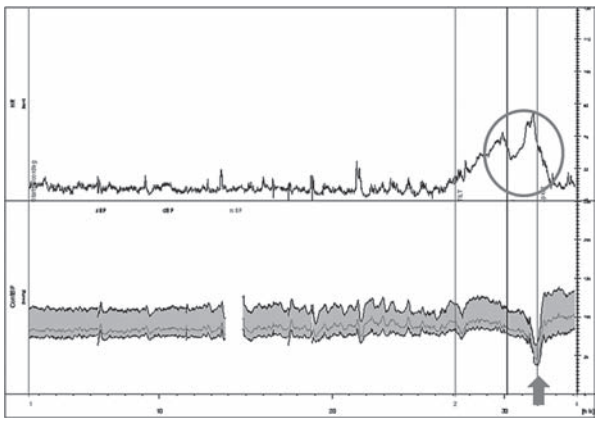

Fig. 4. *Head-up tilt table test in a 90-year-old patient with a history of hypertension and postprandial syncope. Note the decrease in blood pressure (arrow), without decrease in heart rate (circle) typical for the vasodepressor type of syncope.*

typical for ischemia, stress testing, echocardiography and ECG are recommended. HUTT is also used for diagnosis of the postural orthostatic tachycardia syndrome (POTS). Cardinal criteria for this syndrome are symptoms of orthostatic intolerance and absence of orthostatic hypotension (29). For patients with syncope during or after exertion, echocardiography and stress testing are recommended as the first evaluation step. Cardiac pacemaker is recommended in patients with cardioinhibitory syncope with the frequency of seizures more than 5 *per* year (23).

Head-up tilt table test

HUTT helps the diagnosis of different types of dysautonomia. It is used in younger patients with no obvious or suspected heart disease with recurrent syncope of unknown origin, for distinction between syncope with myoclonic jerks and epilepsy, and for the evaluation of patients with unexplained falls or psychiatric disease (5).

Pharmacological agents are used for provocation of positive test results. Isoproterenol is often used to increase vasovagal response. Other agents used in tilt table testing are adenosine (vasodilator and direct activator of the sympathetic system), nitroglycerin and edrophonium (cholinergic activity) (4). The sensitivity of tilt-up test is 26%-80% and specificity 90% (30).

Patients should be in the horizontal position before testing and during HUTT under the angle of 60° to 80° for 30 to 45 minutes (30). If there is no pathological event and vital signs are normal, the test is repeated with pharmacological provocation. The most common protocol is infusion of isoproterenol or administration of sublingual nitroglycerin. The test is considered positive if the patient has a symptomatic decrease in systolic blood pressure and bradycardia. The room must be equipped with resuscitation equipment. Patients must not consume fluids for at least four hours and solid food for at least six hours before the test (32). During testing, the patient's condition is monitored by ECG and continuous noninvasive blood pressure measurement. In patients older than 40 years with a history of syncope, carotid sinus massage is advised (33). The VAsovagal Syncope International Study (VASIS) classification (34) is used for interpretation of the HUTT (Table 1).

Pain provoked HUTT (PP-HUTT) is a test for confirmation of VVS. The subjects are tilted to 70° for a maximum period of 10 min or until symptoms occur. If there are no symptoms after the initial 10 min, a painful stimulus with subcutaneous insertion of 0.7 mm needle into the dorsum of the hand is performed. This test has a sensitivity of 65.9% and specificity of 89.7%. Compared to other tests, such as Calgary Syncope Symptom Score, it has a higher diagnostic rate and provides a rapid alternative to conventional methods (35).

TREATMENT

Treatment approaches are mostly empirical and symptomatic. Specific treatment cannot be made without knowing the cause of syncope. Major therapeutic innovations in recent years are isometric backpressure maneuvers and compression of lower limbs, while most of the drugs do not have great performance. The basis of the treatment of young patients with VVS is education about the potential causes of syncope. In elderly patients, specific treatment is often necessary. The main goal of treatment is to reduce the number of syncopes and psychological trauma.

The first step in the treatment should be an informative talk with the patient about the nature and prognosis of syncope. The patients need to be educated about avoiding heat, prolonged standing and decreased fluid intake. Substitute salt intake and isotonic drinks increase the circulating blood volume and thus venous return. Education includes information about prodromal symptoms and how they can be prevented by sitting or lying. Backpressure maneuvers such as clamping of the arms or leg crossing can inhibit the VVS by increasing the venous return (23).

Rare episodes of syncope with prodromal warning symptoms do not require intervention except for patient observation. In addition, it is important to maintain sufficient fluid and salt intake, especially during summer. Many drugs have been tested in the treatment of VVS, such as β-blockers, disopyramide, scopolamine, theophylline, ephedrine, midodrine, clonidine and SSRI, but there are no clear data on the gold standard therapy (22).

The most commonly used pharmacological agents are β-blockers, anticholinergics, disopyramide, adenosine receptor blockers, SSRI, α-adrenergic agonists, mineralocorticoids, anticonvulsants, and permanent pacemaker as a non-pharmacological treatment (5). These drugs are mainly symptomatic treatment and are often associated with side effects, which make them inappropriate in younger age groups. Fludrocortisone, midodrine and compres-

sion stockings are frequently used in the initial treatment of patients with borderline low pressure and the consequent orthostatic syncope. β-blockers have been the first choice in the treatment for a number of years. According to the guidelines of the European Society of Cardiology, β-blockers should not be used for the treatment of reflex syncope (5). Midodrine effects smooth muscle cells of arteries and veins without affecting heart rate and has no effect on the central nervous system (30). In three randomized, placebo-controlled trials, midodrine had a positive effect on reducing the frequency of symptoms, symptoms during HUTT and quality of life (35). SSRI, in contrast to the vasoconstrictor, can reduce the activity of the sympathetic nervous system (36). Some studies show that SSRI can reduce the incidence of VVS. Results showed that 17.6% of patients who received paroxetine had repeated syncope compared with 52.9% in the placebo group (37).

CONCLUSION

Vasovagal syncope is the most common cause of transient loss of consciousness, especially in younger patients. It is mostly associated with benign prognosis but if it recurs often, it greatly affects the patient's quality of life. The diagnostic and therapeutic goal is correct diagnosis, reduction in the number of episodes, and better quality of life.

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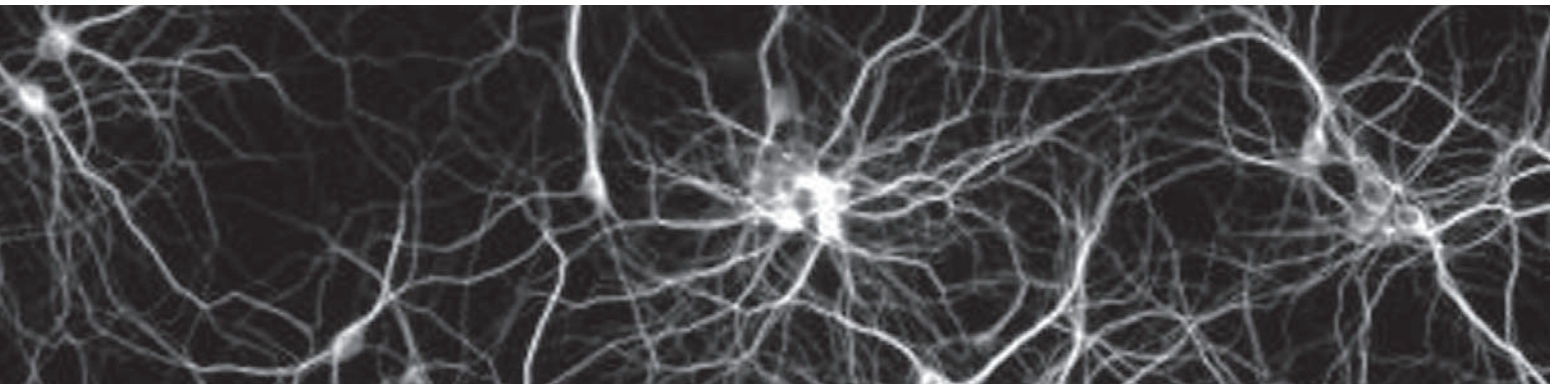
Neuralno posredovana sinkopa

SAŽETAK - Neuralno posredovana ili vazovagalna sinkopa je najčešći uzrok prolaznog gubitka svijesti. Pretjerana reakcija na različite podražaje (emocionalni stres, vađenje krvi, dugotrajno stajanje i sl.) rezultira kratkim i prolaznim gubitkom svijesti uzrokovanim padom krvnog tlaka sa ili bez istovremenog pada srčane frekvencije i posljedičnom prolaznom cerebralnom hipoksijom. Česti prodromalni simptomi su osjećaj mučnine, znojenje, bljedilo, sužavanje vidnog polja. Iako je poznato kako je u podlozi sinkope disregulacija fiziološke kontrole krvnoga tlaka, patofiziologija tog poremećaja još je nejasna. Kontrola krvnog tlaka uključuje složene aferentne signale iz luka aorte koji se obrađuju u središnjem živčanom sustavu te eferentnu modulaciju srčane funkcije i funkcije vaskularnog sustava. Vazovagalna sinkopa obično ne zahtijeva liječenje. No, u slučaju kada treba isključiti druge uzroke gubitaka svijesti, poput srčanih aritmija, potrebna je šira dijagnostička obrada i tada se se najčešće koristi "*head-up tilt table*" test. Česte vazovagalne sinkope nepovoljno utječu na kvalitetu života te je tada moguće uvesti farmakološku terapiju β-blokatorima, npr. metoprololom, selektivnim inhibitorima ponovne pohrane serotonina ili vazokonstriktorima α-agonistima. Preporučuju se vježbe za donje ekstremitete, nošenje kompresivnih čarapa, povećani unos tekućine i soli u prehrani. U težim slučajevima vazovagalnih sinkopa s bradikardijom ili asistolijom postoji mogućnost ugradnje srčanog stimulatora.

Ključne riječi: bradikardija, *head-up tilt table* test, hipotenzija, neuralno posredovana sinkopa



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 vasodilation 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*

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 dented 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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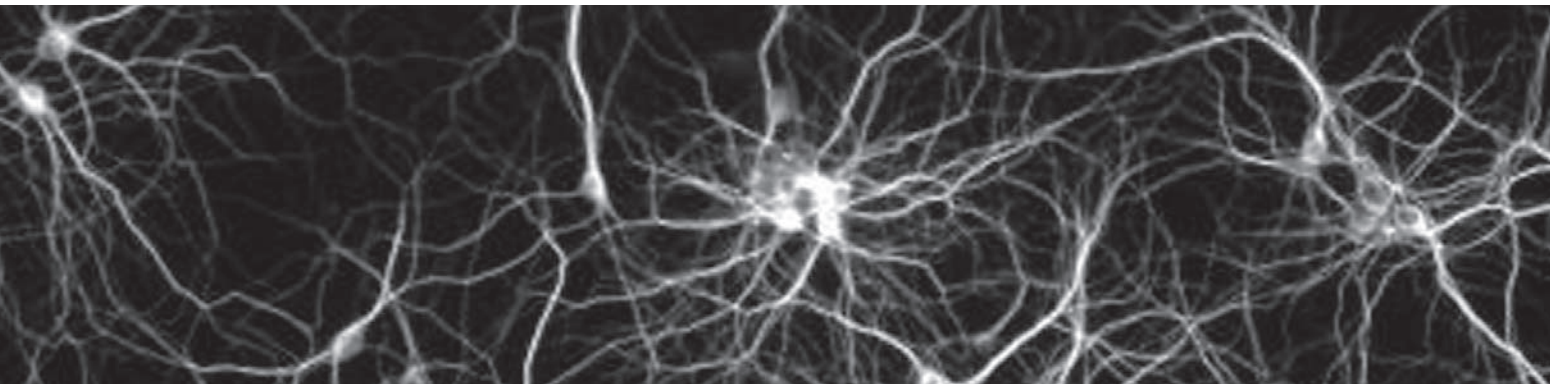
Erektilna disfunkcija u bolesnika s neurološkim poremećajima

SAŽETAK - Erektilna 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 erektilnu disfunkciju ima 1/3 odraslih muškaraca. Erektilna 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. Erektilna disfunkcija je značajni dio kliničke slike neuroloških bolesnika pa je kao dio kliničkog pregleda potrebno promovirati ispitivanje o seksualnim funkcijama.

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



Creutzfeldt-Jacob disease: conventional brain MR imaging findings

H. Aydın, H. Sargin[1], I. Gunes Tatar, V. Kızılgoz, B. Hekimoğlu

ABSTRACT - Sporadic Creutzfeldt-Jacob disease (CJD) is a rare fatal neurodegenerative prion disease. Clinical findings of CJD consist of a rapid onset dementia, myoclonus, and neurologic disorders. Definitive diagnosis is established with histopathologic confirmation of brain parenchyma or autopsy materials. Periodic triphasic electroencephalography (EEG) changes and detection of 14-3-3 protein in cerebrospinal fluid are subsequent diagnostic criteria. A case of a 63-year-old female with painful rigidity, noncooperation, disorientation and bilateral postural tremor is reported. She had hypoactive deep tendon reflexes, moderate agitation, and drowsiness without any facial asymmetry. Her speech was extremely dysarthric and unintelligible, along with akinetic mutism. This case of sporadic CJD is presented with magnetic resonance imaging, EEG results, clinical history and laboratory findings.

Key words: electroencephalography; Creutzfeldt-Jacob disease, sporadic; magnetic resonance imaging, diffusion

INTRODUCTION

Creutzfeldt-Jacob disease (CJD) is a rare fatal neurodegenerative disease caused by deposition of infectious protein called prion in the brain (proteinaceous infectious particle lacking functional nucleic acid, pathologic isoform of prion protein PrPSc-Sc indicates scrapie) (1). It is usually characterized by rapidly progressive dementia, ataxia, myoclonus and other neurologic disorders such as visual disturbances. Electroencephalography (EEG) is characterized by periodic sharp wave complexes and intermittent rhythmical delta activity, but unfortunately we currently do not have any treatment except for palliative symptomatic and supportive one (1,2). The incidence of CJD is 1/1 000 000/year, mean age at onset is usually around 60 years, with 6- to 24-month surveillance after clinical diagnosis (1-5). Sporadic CJD accounts for 85%-90% of all cases, while the remaining 10%-15% belong to the familial, iatrogenic and variant CJD (1,5,6).

Current diagnostic criteria for CJD require demonstration of the specific neurologic symptoms

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combined with characteristic EEG changes in addition to the presence of 14-3-3 protein in the cerebrospinal fluid (CSF). EEG and CSF 14-3-3 protein demonstration have sensitivities ranging of 53%-90% and specificities of 85%-100% (1-7). Recent studies have shown that magnetic resonance imaging (MRI) has a reasonable sensitivity of 60%-90% and high specificity of 95% in depicting CJD (5-7). MRI revealed diffuse cortical atrophy, symmetric or unilateral hyperintensities in the basal ganglia, cerebral cortex and thalamus on T2 weighted (T2W) images, and cortical ribboning (1,2,6,7). Diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) imaging may improve the sensitivity of routine MRI in the detection of neuro-parenchymal abnormalities, especially in the subcortical parts and neocortex (4,5,8).

In this article, brain MRI of a probable sporadic CJD case will be presented. The diagnosis was based on clinical history and presentation, EEG and laboratory findings, as well as MRI results, which were in concordance with the World Health Organization (WHO) clinical diagnostic criteria (1-3,6,7).

CASE REPORT

A 63-year-old female with complaints of altered balance, gait disturbances and anxiety, without any history of trauma, presented to our hospital. Her symptoms started in April 2011, and she had normal brain computed tomography (CT) scan and electromyography (EMG) at that time. She initially had psychiatric consultation and was treated with Solian (Amisulpride), without any benefit. She was referred to the Neurology Department in July 2012 and therapy with Akineton (Biperiden)-Madopar (Carbidopa) was initiated. Despite this treatment, her clinical presentation worsened, so she was admitted to the Hacettepe University Hospital in December 2012 due to increasingly akinetic state, myoclonic jerks and generalized seizure. During that time, the patient was uncooperative and disoriented, while neurologic examination revealed painful rigidity and bilateral postural tremor. She had hypoactive Babinski, deep tendon reflex. She showed moderate agitation, drowsiness without any facial asymmetry, and her extraocular movements were intact.

The pupils were isochoric at midline with normal direct and indirect light reflexes, her speech was extremely dysarthric and unintelligible, without any visual hallucination and insomnia; meanwhile, she showed positive response to auditory and tactile stimuli. From day 4 of her hospital stay, the patient developed akinetic mutism, EEG revealed generalized slow waves, 5-6 Hz tetra frequency waves in background activity without any short interval triphasic periodic wave discharge and epileptic discharges. Control EEG taken one week later predicted the same slow waves with vigilance,

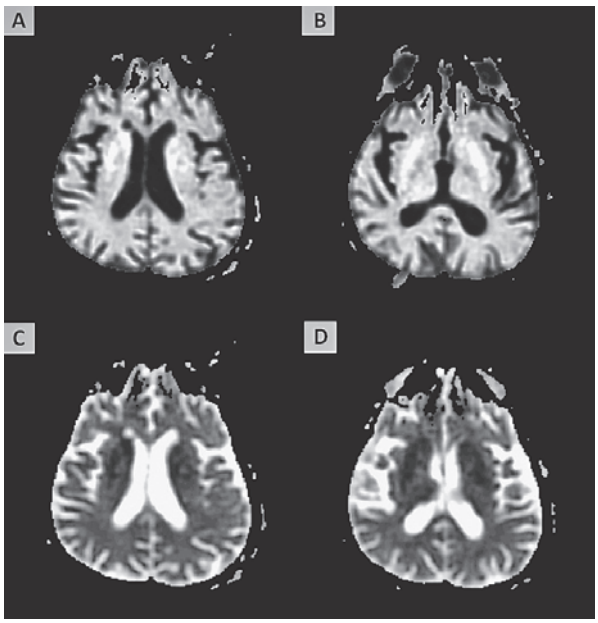

Fig. 1a-b. *Brain MRI taken on January 7, 2013: restricted diffusion demonstrated in basal ganglia and periventricular white matter on DWI and ADC images.*

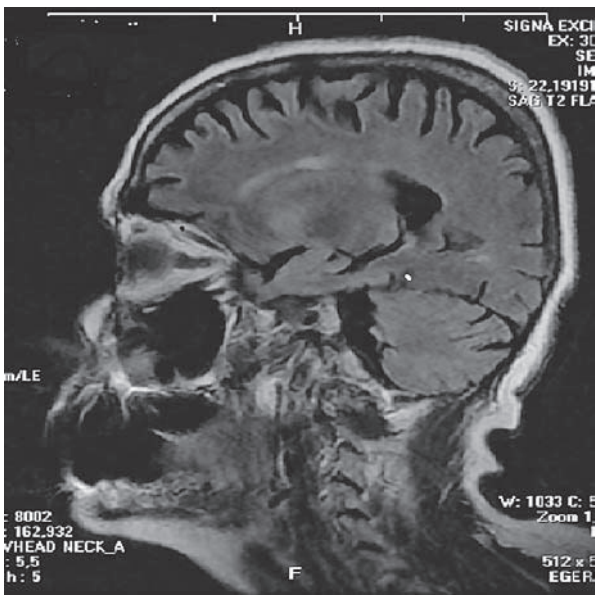

Fig. 2. *In sagittal FLAIR sequence, symmetric basal ganglia and white matter hyperintensities were also evident.*

most prominent in frontal hemisphere. She had no abnormality on EMG. MRI of the brain taken 15 days after admission to the hospital revealed diffusion restriction on bilateral caudate, putamen and cingulate gyri, on FLAIR images; symmetric confluent basal ganglia hyperintensities were observed (Fig. 1a-b, Fig. 2). CSF analysis showed elevated protein (62 mg/dL; normal range 0-10 mg/dL), normal glucose and no pleocytosis, with positive 14-3-3 protein on Western blot CSF. No abnormality could be detected in laboratory tests and general physical examination.

In differential diagnosis, infectious or limbic encephalitis, paraneoplastic syndrome, epilepsy or Alzheimer-like dementia were considered, nevertheless, she had negative NMDA paraneoplastic receptor antibodies (NMDAR Ab) with normal glucose and electrolytes, without any leukocytes or lymphocytes in CSF and no viral panels microbiologically. The possibility of sporadic CJD was accepted, as she had no family history, no family CJD gene and long-lasting clinical presentations. She was discharged from the hospital with brain MRI follow-up due to her refusing longer hospitalization, with partial recovery of her general condition and complaints. She was prescribed Beparine (bemiparin sodium) and Protonix (pantoprazole sodium) on routine follow-up for symptomatic relief and supportive treatment.

Follow-up MRI taken one month later showed further diffusion restriction of the cingulate gyri, putamen and caudate nucleus symmetrically, with acute increasing thalamic diffusion restriction (Fig. 3). These long-lasting diffusion restrictions of basal ganglia and thalamus were also important markers of CJD in this patient. There was no cortical ribboning, no neocortical and limbic involvement, while precentral gyrus-precuneus-angular and parahippocampal areas-mesial cortex were relatively spared on MRI.

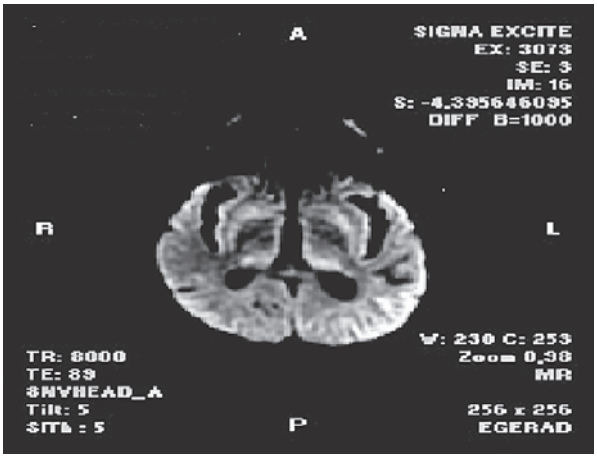

Fig. 3. *Control brain MRI taken on February 6, 2013: restricted diffusion in bilateral thalamus was clearly depicted on DWI images.*

DISCUSSION

CJD is a fatal progressive prion disease characterized by atypical triad of rapidly progressive dementia, myoclonus manifesting as a response to auditory and tactile stimuli, and typical EEG findings (periodical sharp and slow wave complexes) (1,2,7,9).

Recently, MRI and 14-3-3 protein immunoassay in CSF have been established as valuable progressing tools in the diagnosis of suspected CJD cases. MRI generally reveals bilateral hyperintense areas predominantly in the basal ganglia, mild cerebral atrophy, increased signal in the cerebral cortex (cortical ribboning) with 67%-93% sensitivity and specificity (5,7,10). Zerr *et al.* (11) showed sensitivity of 94% and specificity of 84% of protein 14-3-3, however, this protein can also be detected in viral encephalitis, Hashimoto encephalitis, amyotrophic lateral sclerosis, and other types of dementias (2,5,7,12-14). Besides 14-3-3 protein, markers such as neuron-specific enolase, amyloid beta, tau protein, astrocytic protein S 100 and neopterin have also been investigated (2,6,9,12,15). Steinhoff *et al.* (13) report on the sensitivity of 64% and specificity of 91% for EEG examinations in the diagnosis of CJD, while Zerr *et al.* (11) found a sensitivity of 66% and specificity of 74% of EEG in terminal stages, where myoclonus is absent.

In previous reports, DWI and FLAIR images have also been suggested for the suspected diagnosis of CJD, mostly restricted diffusion in the cerebral cortex and subcortical structures in DWI and extensive abnormal hyperintensity in cortical gray matter, accompanying lenticulo-striatal abnormality with or without thalamic abnormality in FLAIR imaging, strongly predicted the diagnosis of CJD (4,5,9,12-15). Mostly, the neocortex-corpus striatum-limbic cortex and thalamus were abnormally involved: frontal lobes were most often affected, followed by parietal and temporal lobes (5,13,16). Symmetric bilateral involvement, predominantly on the anterior striatum while sparing globus pallidus was a frequent sign, and pulvinar sign in case of bilateral posterior thalamic involvement might help in diagnosing variant CJD with high signal at pulvinar and thalamus on FLAIR images (4,5,13,17-19). Primary motor and sensory cortices on either

side of the central rolandic cortex were never identified as abnormal in previous reports of CJD, while primary sensorimotor and visual cortices were always notable exceptions (2,5,15,17,18). Globus pallidus and precentral gyrus hyperintensities were less frequently encountered on FLAIR/DWI, named 'precentral sparing' with diffuse cortical involvement (2,5,7,9,17).

DWI demonstrated markedly more sensitive results than routine MRI and FLAIR imaging. DWI could detect pathology even in the very early stages of the disease, within 3 weeks of the onset of symptoms and before arising of abnormal EEG waves, thus being assumed as an important tool in the early diagnosis of CJD (4,5,8,9,12,13,15). Matoba *et al*. (20) showed that hyperintensities of basal ganglia and neocortex during the early stages were more extensive than in the later stages of the disease in which there was disappearance of abnormal signals in the cortex. Conventional MRI might only reveal discrete abnormalities of the basal ganglia, whereas DWI can demonstrate multifocal regions of hyperintensities in the cerebral cortex in addition to basal ganglia and thalamus, which appeared to be specific for CJD (2,5,6,13,15,17,19).

Shiga *et al*. (12) report on the sensitivity and specificity of 93% for DWI in the diagnosis of CJD, and Young *et al*. (16) on 91% sensitivity and 95% specificity for DWI and FLAIR imaging in the diagnosis of CJD, respectively. Vitali *et al*. (5) state that deep white matter hyperintensities, which were more apparent on DWI than FLAIR images, were diagnostic for CJD, whereas reduction of apparent diffusion coefficient (ADC) in the subcortical regions might also support the diagnosis of CJD. The cause for restricted diffusion on DWI could be attributed to the accumulation of abnormal vacuoles in the cytoplasm and microvacuolation neuritic process with accompanying spongiform degeneration of neural parenchyma histopathologically, while deposition of prion protein might restrict free diffusion of water in the cerebrum (3,13,15-19).

A combination of FLAIR and DWI techniques had more than 90% sensitivity, specificity and accuracy in the differentiation of CJD from other dementias. However, confirmation of the CJD diagnosis is definitely based on neuropathologic examination of the brain tissue obtained either by brain biopsy or postmortem sampling (2,5,9,13,16,17).

The present report on our CJD patient contributes to the relevant literature on sporadic CJD, with myoclonic jerks, akinetic mutism, inappropriate behavior, typical synchronous periodic slow EEG waves, presence of 14-3-3 protein in CSF, and typical diffusion restriction in basal ganglia-cingulate gyri and thalamus on DWI, lacking cerebellar and extrapyramidal signs with the presence of dementia. In this case, brain MRI including DWI was performed as a diagnostic tool and in patient follow-up.

CONCLUSION

According to the WHO diagnostic criteria for probable diagnosis of CJD, the presence of specific EEG findings and 14-3-3 protein positivity in CSF samples or presence of at least 2 criteria, including myoclonus, visual disturbances, cerebellar-pyramidal or extrapyramidal findings and akinetic mutism with progressing dementia are needed (2,4,5,13,17). MRI, mainly DWI, a noninvasive screening tool without administration of IV contrast agent, might improve the *in vivo* diagnosis of CJD and could reduce the need of brain biopsy for accurate diagnosis. DWI findings, which were restricted diffusion at basal ganglia, neocortex, subcortical area and thalami, should probably lead to mandatory diagnosis of CJD even at the very beginning of symptoms.

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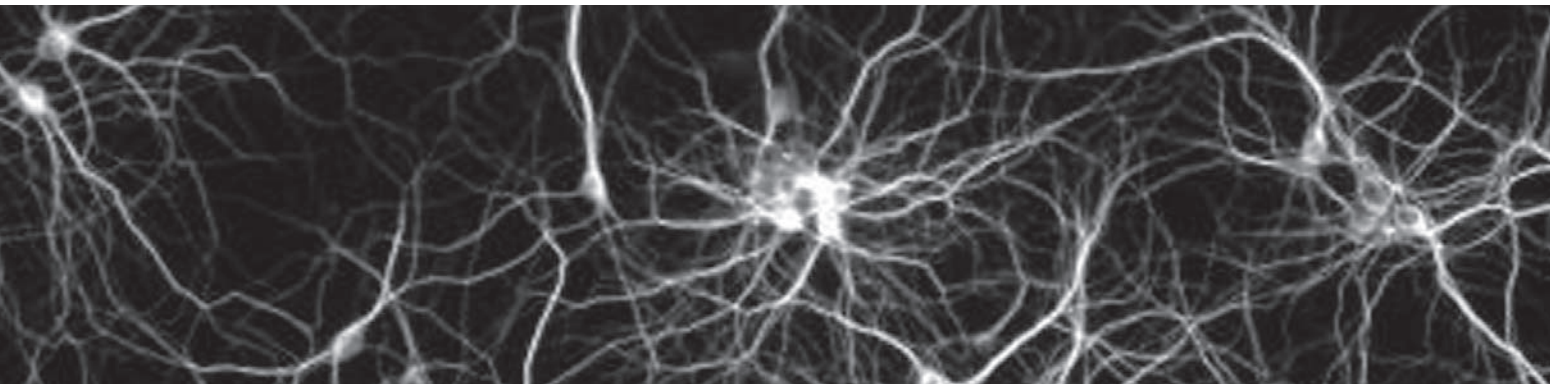
Konvencionalni MRI nalazi u Creutzfeldt-Jakobovoj bolesti

SAŽETAK - Sporadična Creutzfeldt-Jakobova bolest (CJB) je rijetka, fatalna, neurodegenerativna bolest uzrokovana prionom. Klinički nalazi CJB očituju se naglim početkom demencije, mioklonusom, neurološkim poremećajima. Definitivnu se dijagnozu postavlja histopatološkom potvrdom materijala mozga ili materijalom dobivenim autopsijom. Daljnji drugi dijagnostički kriteriji su periodičke trofazne EEG promjene i nalaz proteina 14-3-3 u cerebrospinalnom likvoru. Prikazana je 63-godišnja pacijentica s bolnom ukočenošću, nemogućnošću kooperacije, dezorijentacijom i bilateralnim posturalnim tremorom. Imala je smanjene duboke tetivne reflekse, umjerenu agitaciju, pospanost bez ikakve facijalne asimetrije. Govorila je izrazito dizartrično i nerazgovjetno uz akinetički mutizam. Ovaj slučaj bolesnice sa sporadičnim CJB prikazan je slikovnim prikazom magnetskom rezonancijom, rezultatima EEG-a, poviješću bolesti i laboratorijskim nalazima.

Ključne riječi: EEG, sporadična Creutzfeldt-Jakobova bolest, difuzija, MRI



Genital self-mutilation in a patient with frontotemporal dementia

I. Adamec[1], N. Klepac[1,2], Z. Mubrin[1], M. Habek[1,2]

ABSTRACT - A case of a patient with frontotemporal dementia (FTD) who mutilated his penis is presented. Brain magnetic resonance imaging, single-photon emission computed tomography abnormalities and cognitive assessment are described. Genital self-mutilation (GSM) is a disturbing though yet not described symptom in FTD. A 60-year-old patient presented with a two-year history of social withdrawal and loss of attention to household responsibilities. He was hospitalized and eventually diagnosed with FTD. One day, the nurses observed that his penis was swollen and lacerated. It was discovered that the patient had mutilated his penis with a spoon. He did not have any insight and he completely denied his act. FTD is the second most common cause of dementia in people younger than 65 years. It is characterized by personality changes and impaired social conduct and represents the behavioral variant of the three clinical presentations of frontotemporal lobar degeneration. Sociopathy is a well described but underappreciated phenomenon in FTD patients. It is characterized by decreased insight and decreased awareness of patient's actions and their impact. In patients presenting with behavioral changes and GSM, FTD is one of the diagnoses to be taken in consideration.

Key words: frontotemporal dementia, genital self-mutilation, behavioral changes

INTRODUCTION

Frontotemporal dementia (FTD) is the second most common cause of dementia in patients younger than 65 years (1). It is characterized by personality changes and impaired social conduct and represents the behavioral variant of the three clinical presentations of frontotemporal lobar degeneration (FTLD) (2). These changes are caused by progressive frontal and temporal lobe degeneration (3). Behavioral disturbances vary among patients and there are two distinct behavioral syndromes: the apathetic subtype characterized by generalized loss of interest in activities and volition, loss of social emotions and decreased pain

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response; and the disinhibited subtype characterized by hyperorality, increased preference for sweet foods, exaggerated sensory responses and repetitive motor behavior (4). Patients with FTD commonly violate social norms, for example, by making sexually inappropriate comments, stealing, or public urinating (5). Cognitive impairment is not as pronounced as behavioral changes early in the course of the disease when many patients perform well on traditional neuropsychological tests. As the disease progresses, the number and severity of behavioral changes increase and cognitive impairment emerges, especially concerning executive functioning (6).

Sociopathic behavior has been described in FTD patients and can manifest itself as sexual aggressiveness and inappropriate sexual advances (7). Genital self-mutilation (GSM) has not yet been documented in FTD patients. We report on a patient with FTD developing inappropriate sexual behavior manifesting as mutilation of his penis.

CASE REPORT

A 60-year-old patient presented with a two-year history of social withdrawal and loss of attention to household responsibilities. The patient himself denied having any problems. He had no memory difficulties and was able to manage the household chores. He had 12 years of formal education and had worked as a mechanic. Family history was negative for cognitive or psychiatric disorders.

Physical and neurological examination revealed only positive Babinski sign bilaterally. The patient scored 22/30 on the Mini Mental State Examination (MMSE). Cognitive assessment revealed multiple and severe dysfunctions, mainly in executive and attention tasks. He scored below normal range on digit span forward and backward (test of immediate attention) and Stroop Interference test; Trail A and B tests (tests of executive functions). He also scored in the impaired range on tests of naming and verbal fluency. His memory was still preserved. Results of neuropsychological assessment are presented in Table 1.

Brain magnetic resonance imaging showed bifrontal atrophy. Single-photon emission computed tomography revealed hypoperfusion in bilateral medial frontal and orbitofrontal regions of the cerebral cortex and in cingulate gyri. Cerebrospinal fluid examination revealed elevated tau protein and normal amyloid beta 42 protein levels (Table 2).

Table 1. *Results of neuropsychological assessment*

Test	Score
Mini Mental State Examination Test	22/30
Long- term memory	
Rey auditory- verbal learning test –immediate recall	30/75
Rey auditory -verbal learning test – delayed recall	5/15
Rey–sterrieth complex figure–recall	14/36
Language	
The Boston Naming test	38
Token Test	15/50
Praxis	
Rey–sterrieth complex figure–copy	31/36
Attention and executive functions	
Trail Making test A	65
Trail Making test B	321
Digit span	4
Controlled association letters test	6
The Stroop color-word interference test (mean reading time in seconds for the 24/ item card)	63

Table 2. *Results of cerebrospinal fluid examination*

Test	Result
hTAU Ag	301 ng/L
Phospho TAU (181P)	62 ng/L
Beta-AMILOID (1-42)	565 ng/L

The patient was diagnosed with the behavioral variant of FTLD (2). His behavioral problems progressed during a two-year follow up period and the patient became socially inappropriate with childish attitude. He maintained a stereotyped way of life with little social activity. According to his wife, he showed no sexual interest. Cognitive abilities deteriorated and he developed language difficulty with non-fluent speech. Despite all this, the patient was still functioning on his own and had preserved visuospatial functions. Cognitive assessment was repeated and perseveration and phonemic and semantic paraphasia were noted. He now scored 14/30 on the MMSE. Verbal fluency was greatly reduced as he was able to produce only three words beginning with "S" and 8 animals in one-minute period. On assessment of executive functions, he performed poorly having difficulties with alteration required in Part B of the Trails and incongruent condition of the Stroop task.

At that time, he was admitted to the hospital. During hospital stay, he was seemingly calm but developed paranoia involving his roommate. In the second week of his stay, nurses observed that the glans of his penis was swollen and a hematoma of the orifice of urethra was observed (Fig. 1). A bloody spoon was found at his bedside. Urethroscopy was performed and lacerations of the urethra were found, consistent with injuries from penile insertion of a blunt object. He did not have any insight and completely disregarded his act. Lesions of his penis recovered without sequels and the patient was discharged home.

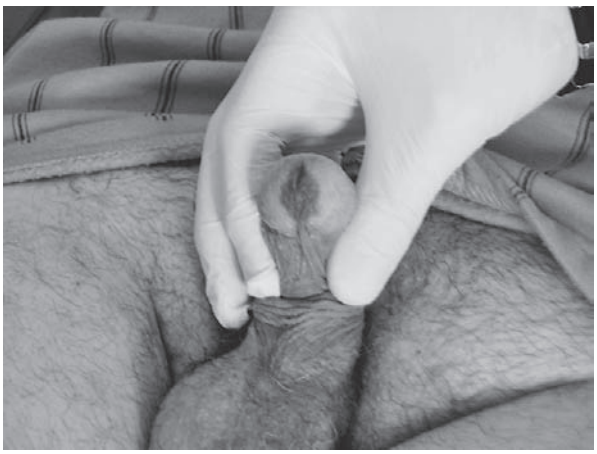

Fig. 1. *Hematoma of the orifice of urethra*

DISCUSSION

The clinical syndrome of FTD is characterized by progressive changes in behavior, personality and/or language, with relative preservation of memory. Profound alterations in behavior can be an early sign and are known to affect personality and social conduct, as well as social inhibition (8). Disinhibition affects domains of interpersonal conduct (i.e. social intrusiveness, rudeness, inappropriate singing and making animal noises), regulation (i.e. inappropriate laughter) and sexual propriety (i.e. inappropriate touching, kissing and grabbing, getting into bed with other patients, public masturbation) (9). Cognitive deficits mainly occur in the domains of attention, planning and problem solving, whereas primary tools of language, perception and spatial functions are well preserved. As the disease progresses, most FTD patients become increasingly disinhibited with a decline of social and interpersonal skills (10).

GSM is an uncommon disorder and is usually described in psychiatric patients, mainly psychotic or intoxicated ones (11). Reviewing the literature, we did not find any description of GSM in patients with FTD. On the other hand, sociopathy is a well described but underappreciated phenomenon in FTD patients. It is characterized by decreased insight and decreased awareness of patient actions and their impact (7). Its pathological paradigm is involvement of the right anterior temporal lobe and right orbitofrontal cortex, which are responsible for acquisition and development of social and moral reasoning and suppression of socially aberrant behavior (12,13). Such emotional and moral deficits are typical for psychotic patients in whom penile self-mutilations have been described. This, we believe, is the psychological platform for the manifested self-mutilation in our patient.

GSM is a disturbing yet so far not described symptom in FTD. In patients presenting with behavioral changes and GSM, FTD is one of the diagnoses to be taken in consideration.

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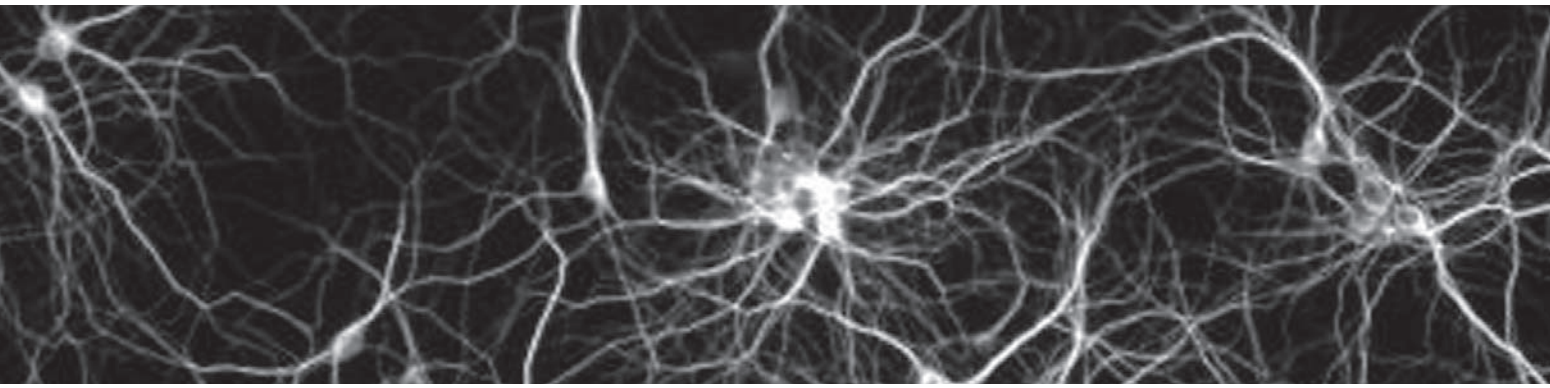
Genitalno samoosakaćenje u bolesnika s frontotemporalnom demencijom

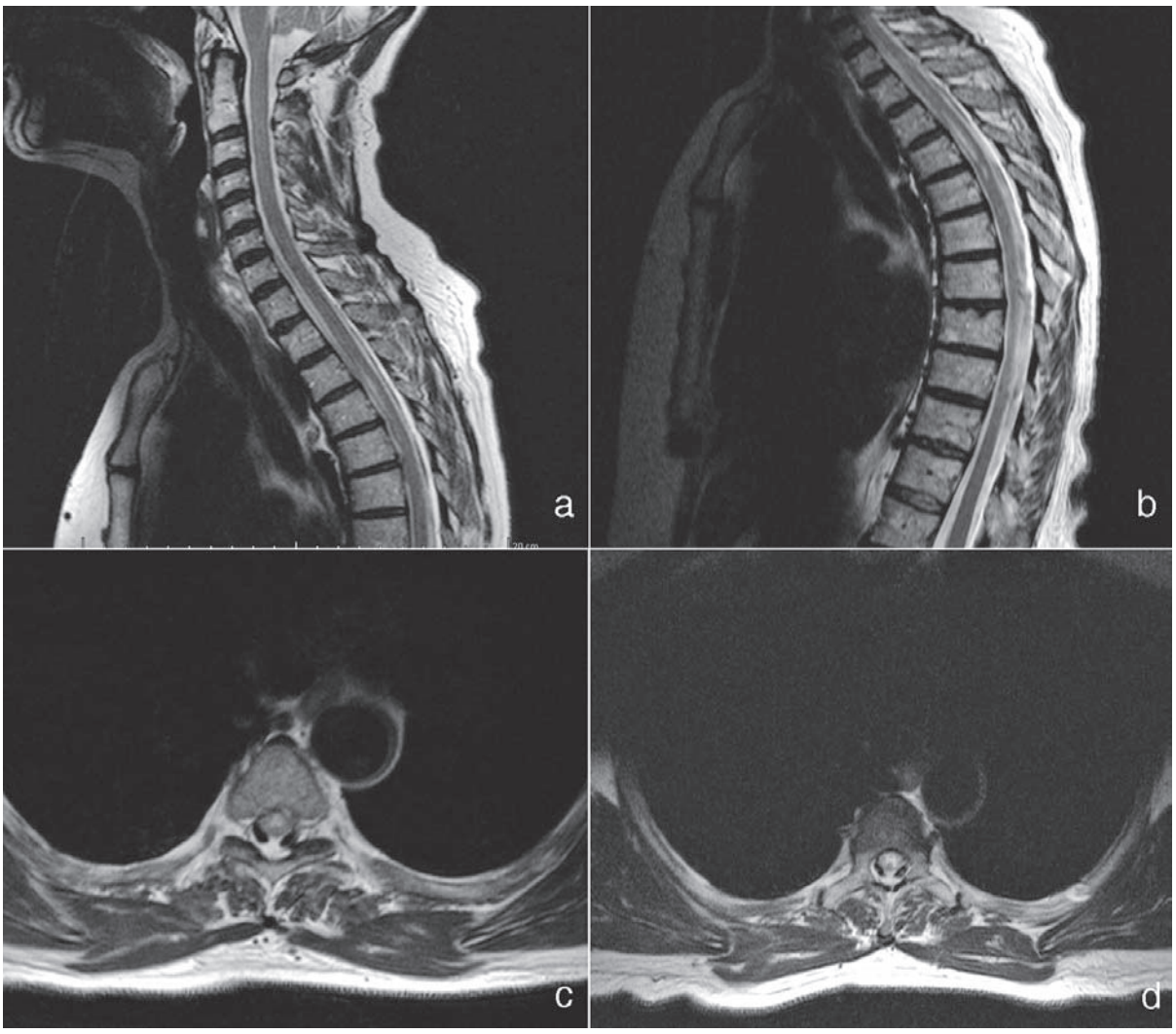
SAŽETAK - Opisan je slučaj pacijenta s frontotempoalnom demencijom (FTD), koji je osakatio svoj penis. Opisane su abnormalnosti mozga otkrivene slikovnim prikazom mozga magnetskom rezonancijom, *single photon* emisijskom kompjutoriziranom tomografijom i kognitivna procjena. Genitalno samoosakaćenje (GSO) je do sada neopisan, ali uznemirujući simptom FTD-a. Bolesnik u dobi od 60 godina bio je unazad dvije godine socijalno povučen i nije obraćao pozornost ni na kakav posao u domaćinstvu. Bio je hospitaliziran i utvrđena je dijagnoza FTD-a. Jednog su dana medicinske sestre opazile da mu je penis natečen i ozlijeđen razderotinom. Otkriveno je da je pacijent žlicom osakatio svoj penis. On nije za to mario i u potpunosti zanijekao taj čin. FTD je drugi najčešći uzrok demencije u ljudi mlađih od 65 godina. Karakteriziraju ga promjene osobnosti i oštećeno socijalno ponašanje i predstavlja bihevioralnu varijaciju triju kliničkih ispoljavanja degeneracije frontotemporalnog režnja. Sociopatija je dobro opisan, ali podcijenjen fenomen u bolesnika s FTD-om. Karakteriziraju je smanjeni uvid i smanjena svjesnost pacijenta o svojim aktivnostima i njihov međusobni utjecaj. Kod pacijenata s promjenama ponašanja i GSO treba pomisliti i na dijagnozu frontotemporalne demencije.

Ključne riječi: frontotemporalna demencija, samoosakaćenje genitalija, promjene ponašanja



Spinal Cord Infarction

I. Adamec, M. Habek



Clinical Department of Neurology, Zagreb School of Medicine and Zagreb University Hospital Center, Zagreb, Croatia

A 69-year-old woman developed acute pain between shoulders and paraparesis. Neurological examination revealed paraparesis (muscle strength 2/5, reflexes 1+, negative Babinski sign). She had sensory level at Th10, with decreased pain and temperature sensation but preserved vibration and position sensation and urinary retention. Spinal cord magnetic resonance imaging (MRI) revealed T2 hyperintense lesion (a and c) from Th3-Th5 level localized in the anterior two-thirds of the cord, predominantly in the gray matter. Repeated spinal cord MRI two days later (b and d) showed further delineation of the lesion. Clinical characteristics of the spinal cord infarction are spared vibration and position sensation. As sensory level may be caudad to the lesion because of the superficial location of the lateral spinothalamic tracts, MRI is crucial imaging modality that can identify the extent of the spinal cord damage. After hospitalization and lengthy physical rehabilitation, the patient was able to walk with help.

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