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THE EFFECT OF STRESS HORMONES ON CEREBRAL HEMODYNAMICS IN PATIENTS WITH CHRONIC POSTTRAUMATIC STRESS DISORDER

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SUMMARY – The aim of the study was to assess the possible correlation between catecholamine and cortisol levels and changes in cerebral hemodynamics in patients with chronic posttraumatic stress disorder (PTSD). The study included 50 patients with chronic PTSD first ever hospitalized for psychiatric treatment and 50 healthy control subjects. All study subjects were aged 30-50. In PTSD patients, 24-h urine levels of the epinephrine and norepinephrine metabolites vanillylmandelic acid (VMA) and cortisol were determined and transcranial Doppler ultrasonography was performed on day 1 of hospital stay and repeated after 21-day psychiatric medicamentous treatment. On initial testing, increased level of 24-h VMA, decreased cortisol level and elevated mean blood flow velocity (MBFV) in the circle of Willis vessels were recorded in 25 (50.00%) patients. Repeat findings obtained after 21-day psychopharmaceutical therapy showed increased 24-h VMA, decreased cortisol and elevated MBFV in the circle of Willis vessels in seven (14.00%) patients (initial *vs.* repeat testing, P=0.0002). Such parameters were not recorded in any of the control subjects (initial PTSD patient testing *vs.* control group, P=0.0000). Study results pointed to a significant correlation between increased catecholamine levels, decreased cortisol level and elevated MBFV in the circle of Willis vessels caused by cerebral vasospasm. Psychiatric medicamentous therapy administered for three weeks significantly reduced the proportion of patients with concurrently altered cerebral hemodynamics, increased levels of catecholamine metabolites and decreased level of cortisol.

Key words: *Stress disorders, post-traumatic; Stress disorders, post-traumatic – physiopathology; Cerebrovascular circulation – physiology; Cerebral hemorrhage – etiology; Cerebral hemorrhage – physiopathology; Cerebral hemorrhage – ultrasonography; Hemodynamic processes – physiology*

Introduction

Although mental disturbances in war veterans were observed as early as the 19th century, indepth research into the posttraumatic stress disorder (PTSD) was only initiated after World War II[1-3]. Considering the growing rate of traumatic events in today's world (natural disasters, traffic accidents, marine and air disasters, wars, terrorist attacks, murders, rape, etc.) that are associated with potent traumatic stressors, PTSD has become one of the major public health problems[4,5]. Physical manifestations of stress accompanied by mental disturbances and clinical picture of chronic PTSD are well known. In patients with

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chronic PTSD, increased sympathetic activity is manifested by elevated blood pressure, enhanced pulse rate and hyperventilation[6,7]. Elevated level of vanillylmandelic acid (VMA) as a catecholamine end metabolite and reduced level of cortisol have been demonstrated in chronic PTSD patients[8,9]. Transcranial Doppler (TCD) changes in terms of elevated mean blood flow velocity (MBFV) in the circle of Willis vessels have also been reported. The frequency spectrum characteristics and parameters of frequency spectrum analysis pointed to cerebral vasospasm[10,11]. In addition, other risk factors for cerebrovascular disease, e.g., cigarette smoking, alcoholism, arterial hypertension, hyperlipidemia and diabetes mellitus, are known to be more frequently present in chronic PTSD patients, favoring the development of atherosclerotic process and cardiovascular impairments[12-16]. These new concepts pose the need of target studies and long-term monitoring of patients with chronic PTSD. The aim of the present study was to identify the possible correlation between catecholamine and cortisol levels and the above mentioned changes of cerebral hemodynamics in chronic PTSD patients, and to monitor the effects of psychiatric medicamentous treatment on these parameters.

Patients and Methods

The study included 50 Croatian war veterans aged 30-50 years. Before the war, they were free from any mental or somatic diseases. The diagnosis of PTSD according to DSM-IV and ICD-10 diagnostic criteria[17,18] was made by a psychiatrist on the basis of a psychological test. The findings of heart and lung x-ray, electrocardiography and extracranial color Doppler of carotid and vertebral arteries were normal in all study patients. The patients were hospitalized at Department of Psychiatry, Dr. Josip Benčević General Hospital in Slavonski Brod, Croatia. Control group consisted of 50 age-matched subjects that had not been engaged in war actions and did not suffer from PTSD or any other psychiatric disorder. During the war, these subjects were living in areas free from war actions.

On day 1 of admission, VMA and cortisol levels in 24-h urine were determined and TCD of cerebral circulation was performed in study patients. Patients having taken banana, vanilla, chocolate, coffee or alcohol in the preceding three days and those on corticosteroid therapy were excluded for the possible influence on 24-h VMA and cortisol levels. Laboratory testing for adrenomedullary hormones was done by measuring the catecholamine end metabolite VMA in 24-h urine. Cortisol as a stress hormone was also determined in 24-h urine. Diurnal oscillations in the catecholamine and cortisol secretion and the impact of daily stressful situations that may increase their production were obviated by circadian measurement of the study parameters. Normal VMA level in 24-h urine is 10-35 μmol/dU; levels greater than 35 μmol/dU are considered as being elevated. Normal cortisol level in 24-h urine is 55-276 nmol/dU; levels lower than 55 nmol/dU are considered as being decreased. TCD examination included measurement of MBFV in the circle of Willis vessels. Cerebral hemodynamics was assessed by use of an EME Trans-scan 3D device with a 2 MHz probe. Standardized MBFV values expressed in centimeters *per* second (cm/s) were used. Elevated MBFV with typical frequency spectrum extensions were considered as reflecting cerebral vasospasm as a consequence of prolonged contraction of the cerebral artery smooth muscle walls[19-21].

The examinations were repeated after 3-week hospital stay and psychiatric treatment with antidepressants and anxiolytics. These findings were compared with those from initial testing and with findings recorded in the control group of healthy subjects.

On statistical analysis, the test of proportion between two groups was employed, with the level of significance set at $P<0.05$. Based on the results obtained, correlation of particular subject groups with elevated catecholamine levels and changes in cerebral hemodynamics was determined.

Results

Initial measurements showed concurrent 24-h VMA increase, 24-h cortisol decrease and presence of cerebral vasospasm in 25 of 50 (50.00%) patients with chronic PTSD. Upon 3-week psychopharmacotherapy, the same pattern of study parameters was recorded in seven (14.00%) patients. The difference was statistically significant ($P=0.0002$) (Table 1). None of the control group subjects had concurrently elevated 24-h VMA, decreased 24-h cortisol and cerebral vasospasm. Difference between chronic PTSD

Table 1. Concurrent determination of elevated VMA, decreased cortisol and cerebral vasospasm in PTSD patients: initial testing vs. *repeat testing*

Group	Elevated VMA + decreased cortisol + vasospasm	Other	Total
PTSD patients Initial testing	25 (50.00%)	25 (50.00%)	50 (100.00%)
PTSD patients Repeat testing	7 (14.00%)	43 (86.00%)	50 (100.00%)

P, test of proportion; *P*=0.0002; PTSD = posttraumatic stress disorder; VMA = vanillylmandelic acid

Table 2. Concurrent determination of elevated VMA, decreased cortisol and cerebral vasospasm: PTSD patient initial testing vs. *control group*

Group	Elevated VMA + decreased cortisol + vasospasm	Other	Total
PTSD patients Initial testing	25 (50.00%)	25 (50.00%)	50 (100.00%)
Control group	0 (0.00%)	50 (100.00%)	50 (100.00%)

P, test of proportion; P=0.0000; PTSD = posttraumatic stress disorder; VMA = vanillylmandelic acid

Table 3. Concurrent determination of normal VMA, normal cortisol and cerebral vasospasm in PTSD patients: initial testing vs. *repeat testing*

Group	Normal VMA + normal cortisol + vasospasm	Other	Total
PTSD patients Initial testing	2 (4.00%)	48 (96.00%)	50 (100.00%)
PTSD patients Repeat testing	1 (2.00%)	49 (98.00%)	50 (100.00%)

P, test of proportion; *P*=0.5591; PTSD = posttraumatic stress disorder; VMA = vanillylmandelic acid

Table 4. Concurrent determination of normal VMA, normal cortisol and cerebral vasospasm: PTSD patient initial testing vs. *control group*

Group	Normal VMA + normal cortisol + vasospasm	Other	Total
PTSD patients Initial testing	2 (4.00%)	48 (96.00%)	50 (100.00%)
Control group	2 (4.00%)	48 (96.00%)	50 (100.00%)

P, test of proportion; *P*=1.0000; PTSD = posttraumatic stress disorder; VMA = vanillylmandelic acid

patients and control subjects was statistically significant (*P*=0.0000) (Table 2). In the group of chronic PTSD patients, normal levels of 24-h VMA and 24-h cortisol with the presence of cerebral vasospasm were recorded in two (4.00%) patients on initial testing and in one (2.00%) patient on repeat testing; the difference did not reach statistical significance (*P*=0.5591) (Table 3). As normal levels of the same parameters were

recorded in two (4.00%) control subjects, there was no statistically significant difference from the group of chronic PTSD patients (P=1.0000) (Table 4).

Discussion

Patients with untreated chronic PTSD showed a significantly higher rate of elevated VMA and decreased cortisol levels, along with a high prevalence of vasospasm in the circle of Willis vasculature. None of the control subjects had such a pattern of study parameters. Although 3-week psychopharmaceutical therapy resulted in significant improvement of the findings in PTSD patients, a significantly higher rate of abnormal findings in comparison to the control group persisted on repeat testing. A high correlation between elevated catecholamine level, decreased cortisol level and cerebral vasospasm was found on both initial and repeat testing.

Chronic PTSD patients have impaired biological response to stress due to failure in the mechanism of negative feedback. In the initial stage of disease, PTSD patients have elevated baseline cortisol level, followed by complete collapse of the hypothalamic-pituitary-adrenal axis in chronic stage of the disease, resulting in decreased baseline cortisol level that now fails to play its physiologic role in stress situation[22-24].

Studies have demonstrated an increased activity of the adrenergic system in stress. Daily stressful situations cause prompt increase of epinephrine and norepinephrine secretion; catecholamine level normalizes soon upon stress cessation[25,26]. In spite of the stressful event having been experienced long before, PTSD patients develop pathologic response to stress, which results in elevated baseline catecholamine levels[27-34]. The increased catecholamine level associated with stress response entails an increase in sympathetic tonus, which is in turn accompanied by clinical signs such as tachycardia, elevated blood pressure, mydriasis, hyperventilation, etc. These patients show a higher rate of elevated blood pressure and increased pulse rate as compared with their healthy age-mates[35-37].

Catecholamine levels normalize soon upon stress cessation, resulting in disappearance of the accompanying clinical manifestations[38]. The findings of elevated 24-h VMA level along with decreased cortisol level have already been reported in PTSD patients[9,39,40]. Our results confirmed these reports and pointed to the value of 24-h VMA and 24-h cortisol determination in untreated PTSD patients before and after therapy introduction.

Our previous studies pointed to increased flow rate in basal cerebral arteries in patients with chronic PTSD, associated with frequency spectrum changes suggestive of vasospasm[10,11]. The central nervous system and the circle of Willis vasculature contain exclusively adrenergic alpha 1 receptors. Stimulation of these receptors induces vasoconstriction and vasospasm[41-44]. Results of the present study confirmed the presence of cerebral vasospasm in the majority of PTSD patients and pointed to the role of TCD as an important diagnostic method for detection and monitoring of hemodynamic changes in cerebral vasculature of chronic PTSD patients.

To the best of our knowledge, there are no literature reports on the study of correlation between elevated VMA levels, decreased cortisol level and cerebral hemodynamics in patients with chronic PTSD, only a functional testing demonstrating relatively rapid change of cerebral perfusion in some physiologic states has been reported. For example, intracranial arterial MBFV increased by 38%-66% from baseline was recorded as early as 3 minutes of cerebral circulation acetazolamide stimulation. The acetazolamide test has proved highly useful in patients with atherosclerotic stenosis of carotid arteries. A higher grade of stenosis correlated with lower vasoreactivity in the ipsilateral cerebral hemisphere[45-47]. Functional brain testing with various cognitive stimuli such as reading, light, sound, visualization, imagined speech, etc., showed MBFV increase in the brain regions activated by the respective stimuli. Upon stimulus cessation, the MBFV returned to basal values[48-51]. Elevated MBFV were also detected in smokers, which is attributed to nicotine receptor stimulation, increased catecholamine secretion and indirectly induced cerebral vasospasm[52]. The highest degree of vasospasm was found in patients with subarachnoid hemorrhage[19-21,53].

Clinical relevance of prolonged cerebral vasospasm found in patients with chronic PTSD has not yet been fully clarified. As PTSD patients have a higher rate of various risk factors for atherosclerosis, such as cigarette smoking, alcoholism, arterial hypertension, obesity, hyperlipidemias, diabetes mellitus, etc., the likelihood of developing atherosclerosis, cerebrovascular and cardiovascular diseases is significantly greater

as compared with general population[12-16,54-56]. Therefore, additional studies of the association between pathophysiologic changes and cerebral circulation in PTSD patients are warranted, along with proper monitoring of long-term somatic PTSD sequels. TCD analysis of cerebral circulation with concurrent determination of 24-h VMA and cortisol levels can help in the diagnosis of chronic PTSD, follow-up of the course of disease and assessment of psychiatric treatment outcome.

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Sažetak

UČINAK STRESNIH HORMONA NA MOŽDANU HEMODINAMIKU KOD BOLESNIKA S KRONIČNIM POSTTRAUMATSKIM STRESNIM POREMEĆAJEM

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Cilj ovoga rada bio je utvrditi moguću povezanost između razine kateholamina, kortizola i promjena cerebralne hemodinamike u bolesnika s kroničnim posttraumatskim stresnim poremećajem (PTSP). Ispitivanjem je obuhvaćeno 50 bolesnika s kroničnim PTSP koji su prvi put hospitalizirani i psihijatrijski liječeni te 50 zdravih ispitanika kontrolne skupine. Svi ispitanici bili su u dobi između 30 i 50 godina. U bolesnika s PTSP su prvoga dana boravka analizirane vrijednosti vanilmandelične kiseline (VMA), metabolita adrenalina i noradrenalina te kortizola u 24-satnoj mokraći i učinjena je transkranijska dopler sonografija (TCD). Isti dijagnostički postupci ponovljeni su nakon 21-dnevnog medikamentnog psihijatrijskog liječenja. Prva analiza pokazala je istodobno povišenu razinu 24-satne VMA, sniženi kortizol i povišene srednje brzine strujanja krvi (SBSK) krvnih žila Willisova kruga u 25 (50,00%) bolesnika. Druga analiza koja je učinjena nakon 21-dnevnog psihijatrijskog liječenja pokazala je istodobno povišenu razinu 24-satne VMA, sniženi kortizol i povišene SBSK krvnih žila Willisova kruga u 7 (14,00%) bolesnika (odnos prve i druge analize P=0,0002), dok u kontrolnoj skupini nije pronađen niti jedan takav ispitanik s navedenim parametrima (odnos prve analize i kontrolne skupine P=0,0000). Istraživanje je pokazalo značajnu povezanost povišene razine kateholamina, sniženog kortizola i povišenih SBSK u krvnim žilama Willisova kruga koje su uzrokovane cerebralnim vazospazmom. Medikamentno psihijatrijsko liječenje PTSP u trajanju od tri tjedna dovelo je do značajnog smanjenja udjela bolesnika s istodobno promijenjenom cerebralnom hemodinamikom, povišenom razinom metabolita kateholamina i smanjenom razinom kortizola.

Ključne riječi: *Stresni poremećaj, posttraumatski; Stresni poremećaj, posttraumatski – fiziopatologija; Cerebrovaskularna cirkulacija – fiziologija; Moždano krvarenje – etiologija; Moždano krvarenje – fiziopatologija; Moždano krvarenje – ultrazvuk; Hemodinamski procesi – fiziologija*