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Effect of Elevated Catecholamine Levels on Cerebral Hemodynamics in Patients With Chronic Post-Traumatic Stress Disorder

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A B S T R A C T

The aim of the study was to assess the correlation between the levels of catecholamines and cerebral hemodynamics in patients with chronic post-traumatic stress disorder (PTSD). The study included 50 patients with chronic PTSD hospitalized for psychiatric treatment for the first time, and 50 healthy control subjects. All study subjects were in the 30–50 age group. In PTSD group, determination of vanllylmandelic acid (VMA), an epinephrine and norepinephrine metabolite, in 24-h urine and transcranial Doppler (TCD) sonography of the circle of Willis vasculature were performed on the first day of hospital stay. The same diagnostic procedures were repeated upon the completion of 21-day medicamentous psychiatric treatment. Initial analysis revealed concurrently elevated 24-h VMA in 29 (58.00%) patients and increased values of the mean blood flow velocity (MBFV) in the circle of Willis vasculature in 34 (68.00%) patients, indicating a high correlation of the respective parameters (p=0.3290). Second analysis performed after 21-day psychiatric treatment showed concurrently elevated 24-h VMA in eight (16.00%) patients and increased MBFV in the circle of Willis vasculature in nine (18.00%) patients, also pointing to a high correlation of the parameters observed (p=0.7906). In the control group, only two (4.00%) subjects had elevated MBFV in the circle of Willis vessels, whereas the level of 24-h VMA was normal in all control subjects. Study results pointed to a significant association between elevated levels of stress hormones and increased MBFV in the circle of Willis vasculature caused by cerebral vasospasm. Medicamentous psychiatric treatment for PTSD administered for three weeks significantly reduced the proportion of PTSD patients with elevated levels of the catecholamine metabolite and cerebral vasospasm. Study results showed a high correlation between diurnal VMA level and elevated MBFV in the circle of Willis vessels, clearly demonstrating the effect of prolonged elevation of catecholamine levels on cerebral hemodynamics.

Key words: *chronic post-traumatic stress disorder, catecholamines, cerebral hemodynamics, transcranial ultrasonography*

Introduction

Behavioral changes in war veterans were recognized as early as the 19th century; however, studies of post-traumatic stress disorder (PTSD) were only initiated after World War II[1–3]. Considering the ever increasing rate of traumatic events in today's world (wars, terrorist attacks, disasters, traffic and rail accidents, marine and air disasters, murder, rape, etc.), which are associated with strong traumatic stressor, PTSD is emerging as a major public health problem[4,5]. The clinical picture of chronic PTSD with mental disturbances and physical manifestations of stress is well known. The manifestations of increased sympathetic activity in patients with chronic

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PTSD include accelerated pulse rate, elevated blood pressure and hyperventilation[6–8]. Increased levels of vanllylmandelic acid (VMA) as an end-product of catecholamine metabolism have been demonstrated in patients with chronic PTSD[9,10]. Changes on transcranial Doppler (TCD) sonography in terms of the mean blood flow velocity (MBFV) increase in the circle of Willis vasculature have been described, with the characteristics of frequency spectra and parameters of spectral frequency analysis indicating cerebral vasospasm[11–13]. Cerebral vasospasm is a result of prolonged contraction of cerebral artery wall smooth muscle cells[14–18].

As other risk factors for cerebrovascular disease such as arterial hypertension, cigarette smoking, alcoholism, hyperlipidemia and diabetes mellitus also show a greater prevalence in chronic PTSD patients, there is a high risk of a precipitated atherosclerotic process and development of cardiovascular disorders[19–25]. These issues pose the need of additional studies and long-term follow up of patients with chronic PTSD.

The aim of the present study was to assess the possible association between catecholamine levels and these specific changes of cerebral hemodynamics in chronic PTSD patients, and to monitor the effect of psychiatric treatment on these parameters.

Patients and Methods

The study included 50 Croatian Army soldiers aged 30–50, actively engaged in the 1991–1995 war. None of the study patients had a pre-war history of mental or somatic disorders. The diagnosis of PTSD was made by a psychiatrist according to DSM-IV and ICD-10 diagnostic criteria[26,27] and psychological testing. Electrocardiography, heart and lung x-ray, and extracranial color Doppler of carotid and vertebral arteries showed normal findings in all study patients, hospitalized for the first time at Department of Psychiatry, General Hospital in Slavonski Brod. Lindergaard's index in all patients were 1,7±0,4; regular. Control group consisted of 50 age-matched male subjects who had not been involved in war actions and were free from PTSD or any other mental disorder. During the war, these subjects were living in areas not affected by war actions.

On day 1 of hospital admission, the level of VMA in 24-h urine was determined and TCD study of cerebral circulation was performed. In order to eliminate a potential laboratory error, patients having taken banana, vanilla, chocolate, coffee and alcohol in the past three days were excluded for the possible effect on 24-h VMA. Laboratory analysis of adrenomedullary hormones was performed by measuring VMA as a catecholamine metabolism end-product in 24-h urine. Diurnal variation in catecholamine secretion and the impact of daily stressors that may enhance their production were obviated by 24-h measurement. The normal range of 24-h urine VMA is 10–35 μmol/dU; the levels exceeding 35 μmol/dU were considered as elevated. TCD study included MBFV measurement in the circle of Willis vasculature, but values of MBFV in arteria cerebri media over 120 cm/sec were take for cerebral vasospasm. The study of cerebral hemodynamics was performed on an EME Trans-scan 3D device with a 2 MHz probe, using standardized MBFV values expressed in centimeters *per* second (cm/s). Elevated MBFV with typically extended frequency spectra were considered to reflect cerebral vasospasm consequential to prolonged contraction of the cerebral arterial wall smooth muscle[28–30].

These studies were repeated after 3-week hospital stay and psychiatric treatment with antidepressants and anxiolytics, and results of the two measurements as well as those recorded in the control group were compared. On statistical analysis, the test of proportion between two groups was employed. The level of statistical significance was set at $p<0.05$. The results thus obtained were used to assess the association of different subject groups with elevated levels of catecholamines and changes in cerebral hemodynamics.

Results

The initial measurement of 24-h VMA showed elevated levels in 29 (58%) chronic PTSD patients and none of the control subjects. The difference was statistically significant ($p=0.0000$) (Table 1). On repeat measurement performed after 3-week psychopharmaceutical therapy, elevated 24-h VMA was recorded in ten (20%) patients. The difference from the initial measurement was statistically significant ($p=0.0000$), pointing to a considerably higher rate of elevated VMA in untreated chronic PTSD patients (Table 2).

In chronic PTSD patients, initial TCD studies were performed upon hospital admission, before the initiation of psychiatric therapy. Elevated MBFV in the circle of

TABLE 1
VMA IN 24-HOUR URINE: FIRST MEASUREMENT: PTSD AND CONTROL GROUP

Examinees	increased VMA	normal VMA	Total
PTSD patients	29 (58.00%)	21 (42.00%)	50 (100.00%)
Control group	0 (0.00%)	50 (80.00%)	50 (100.00%)

p-proportion test; $p=0.0000$

TABLE 2
VMA IN 24-HOUR URINE: FIRST AND SECOND MEASUREMENT IN PTSD PATIENTS

PTSD patients	increased VMA	normal VMA	Total
First measurement	29 (58.00%)	21 (42.00%)	50 (100.00%)
Second measurement	10 (20.00%)	40 (80.00%)	50 (100.00%)

p-proportion test; $p=0.0000$

Willis vasculature was recorded in 34 (68%) patients and two (4%) control subjects, yielding a statistically significant difference (p=0.0000) (Table 3). Repeat TCD studies were obtained after 3-week psychopharmaceutical therapy and revealed vasospasm in only nine (18%) patients. The difference between the two measurements in PTSD patients was statistically significant (p=0.0000), pointing to a considerably greater rate of vasospasm in the circle of Willis vasculature in untreated PTSD patients (Table 4).

Comparison of the subgroups of with the circle of Willis vasospasm and elevated 24-h VMA on initial measurement showed no statistically significant between-group difference (p=0.3290), pointing to the association of the circle of Willis vasospasm and VMA elevation in untreated PTSD patients (Table 5).

The same association was studied between subject subgroups with the circle of Willis vasospasm and elevated 24-h VMA on repeat measurement, yielding no statistically significant between-group difference either (p=0.7906) and pointing to the concurrence of the circle of Willis vasospasm and VMA elevation in PTSD patients (Table 6).

TABLE 3
TCD ANALYSIS OF CEREBRAL CIRCULATION: FIRST MEASUREMENT

Examinees	Vasospasm	Withouth vasospasm	Total
First measurement in PTSD patients	34 (68.00%)	16 (32.00%)	50 (100.00%)
Control group	2 (4.00%)	48 (96.00%)	50 (100.00%)

p-proportion test; p=0.0000

TABLE 4
TCD ANALYSIS OF CEREBRAL CIRCULATION: FIRST AND SECOND MEASUREMENTS

Examinees	Vasospasm	Withouth vasospasm	Total
First measurements of PTSD	34 (68.00%)	16 (32.00%)	50 (100.00%)
Second measurements of PTSD	9 (18.00%)	41 (82.00%)	50 (100.00%)

p-proportion test; p=0.0000

TABLE 5
CORRELATION BETWEEN CEREBRAL VASOSPASM AND INCREASED VMA (FIRST MEASUREMENT)

Examines	N	%	
Vasospasm Willis	34	68.00	
Increased VMA	29	58.00	p=0.3290
Total	50	100.00	

p=0.3290

TABLE 6
CORRELATION BETWEEN CEREBRAL VASOSPASM AND INCREASED VMA (SECOND MEASUREMENT)

Examines	N	%	
Vasospasm Willis	9	18.00	p=0.7906
Increased VMA	8	16.00	
Total	50	100.00	

p=0.7906

Discussion

Patients with untreated PTSD were found to have a considerably higher rate of elevated VMA and the circle of Willis vasospasm than the control group of healthy subjects. Although 3-week psychiatric treatment resulted in a significant reduction of these abnormalities in PTSD patients, they still showed a statistically significantly higher rate in comparison with control group. There was a high correlation between elevated catecholamine levels and cerebral vasospasm on both initial and repeat measurements.

A number of studies have already demonstrated the adrenergic system activity to be enhanced by stress. In spite of the long time that has elapsed since their stress exposure, PTSD patients develop a pathological response to stress, which results in elevated baseline catecholamine levels[31–34]. Such a pathological response was confirmed in the present study, where elevated baseline catecholamine levels were recorded in 58% of PTSD patients. The prevalence of elevated blood pressure and increased pulse rate is statistically significantly greater in these patients than in their healthy age-matched counterparts[35–37]. Other studies have also reported elevated 24-h VMA levels in PTSD patients[38–41]. Our results confirmed these reports and pointed to the role of pre- and post-therapeutic 24-h VMA analysis in untreated chronic PTSD patients. Therapeutic efficacy could be evaluated by monitoring VMA pattern in these patients.

Our previous studies have pointed to increased MBFV in the basal cerebral arteries of patients with chronic PTSD, with changes in the frequency spectra suggestive of vasospasm[11,12]. Results of our study confirmed the presence of cerebral vasospasm in the majority of PTSD patients and pointed to the value of TCD study as a diagnostic method for the detection and monitoring of hemodynamic events in the cerebral vasculature of patients with chronic PTSD.

To the best of our knowledge, there are no studies of the association of elevated VMA levels and cerebral hemodynamics in chronic PTSD patients. There are reports on functional testing demonstrating relatively rapid changes of cerebral perfusion in some physiologic conditions. For example, a 38%–66% MBFV increase from baseline was recorded in intracranial arteries as early as 3 minutes of the cerebral circulation stimulation with acetazolamide. The higher degree of carotid stenosis correlated with poorer vasoreactivity in the ipsilateral

cerebral hemisphere[42]. Induction of functional brain stress induced by various cognitive stimuli such as reading, light, sound, visualization, speech imaging, etc. revealed MBFV elevation in the brain regions activated by the particular stimulus. Upon stimulus discontinuation, the MBFV returned to baseline levels[43–45]. The most pronounced vasospasm was observed in patients with subarachnoid hemorrhage[46].Clinical relevance of prolonged cerebral vasospasm found in patients with chronic PTSD has not yet been fully clarified. As PTSD patients have a higher prevalence of various risk factors for atherosclerosis, e.g., cigarette smoking, arterial hypertension, alcoholism, obesity, hyperlipidemia, diabetes mellitus, etc., they are quite likely to be at a considerably greater risk of atherosclerosis, cerebrovascular and cardiovascular disorders[19–22,47]. Therefore, it is of utmost importance to continue research into the association of pathophysiologic changes in PTSD and cerebral circulation, and to monitor the somatic sequels of PTSD at long term. TCD analysis of cerebral circulation with concurrent evaluation of 24-h VMA can facilitate diagnostic work-up, along with appropriate monitoring of the course of disease and psychotherapeutic efficacy.

REFERENCES

1. MYERS ABR, On the etiology and prevalence of disease of the heart among soldiers (J Churchill, London, 1870). — 2. DA COSTA JM, Am J of the Med Scien, 61 (1871) 17. — 3. OPPENHEIM H, Die traumatiche neurosensation (Hirschwald, Berlin, 1889). — 4. KESSLER RC, J Clin Psychiatry, 61 (2000) 4. — 5. HELZER JE, New Engl J Med, 317 (1987) 1650. — 6. VAN DER KOLK BA, J Clin Psychiatry, 58 (1997) 16. — 7. VAN DER KOLK BA, Hum Psychofarmacol, 16 (2001) 49. — 8. QURESHI SU, PYNE PM, MAGRUDER KM, SCHULZ PE, KUNIK ME, Psychiatr Q, 80 (2009) 87.. — 9. MASON JW, GILLER EL, KOSTEN TR, HARKNESS L, J Nerv Ment Dis, 176 (1988) 498. — 10. PITMAN R, ORR S, Biol Psyciat, 27 (1990) 245. — 11. DIKANOVIĆ M, KADOJIĆ D, BAŠIĆ-KES V, ŠERIĆ V, DEMARIN V, Milit Med, 11 (2001) 955. — 12. KADOJIĆ D, DEMARIN V, KADOJIĆ M, MIHALJEVIĆ I, BARAC B, Coll Antropol, 2 (1999) 665. — 13. CHEN F, WANG X, WU B, Acta Neurochir Suppl, 110 (2011) 233. — 14. ALEXANDROV V, DEMARIN V, Acta Clin Croat, 38 (1999) 97. — 15. LENDEGAARD KF, NORNES H, BAKKE SJ, Acta Neurochir (Wien), 100 (1987) 12. — 16. SLOAN MA, Transcranial Doppler monitoring of vasospasm after subarachnoid hemorrhage. In: TEGELER CH, BABIKIAN VL, GOMEZ CR (Eds) Neurosonology (St. Louis: Mosby, 1996). — 17. NEWELL DW, WINN HR, Neurosurg Clin N Am, 12 (1990) 319. — 18. AASLID R, Europ Jour of Ultrasou, 16 (2002) 3. — 19. KADOJIĆ D, DEMARIN V, KADOJIĆ M, MIHALJEVIĆ I, BARAC B, Coll Antropol, 1 (1999) 213. — 20. KANG HK, BULLMAN TA, TAYLOR JW, Ann Epidemiol, 16 (2006) 381. — 21. GANDER ML, VON KANEL R, Eur J Cardiovasc Prev Rehabil, 13 (2006) 165. — 22. STRAWN JR, EKHATOR NN, HORN PS, BAKER DG, GERACIOTI TD JR, Psychosom Med, 66 (2004) 757. — 23. WEISBERG RB, BRUCE SE, MACHAN JT, KESSLER RC, CULPEPPER L, KELLER MB, Psychiatr Serv, 53 (2002) 848. — 24. MIŠIGOJ-DURAKOVIĆ M, DURAKOVIĆ Z, Coll. Antropol. 33 (2009) 759. — 25. MASLOV B, MARČINKO D, MILIČEVIĆ R, BABIĆ D, ĐORĐEVIĆ V, JAKOVLJEVIĆ M, Coll. Antropol. Suppl. 2 33 (2009) 7. — 26. HRVATSKI ZAVOD ZA JAVNO ZDRAVSTVO, MKB-10 (Medicinska naklada, Zagreb, 1994). — 27. AMERIČKA PSIHIJATRIJSKA UDRUGA, DSM-IV (Naklada Slap, Jastrebarsko, 1996). — 28. MAYBERG MR, Neurosurg North Am, 9 (1998) 615. — 29. BARKER FG, HEROS RC, Neurosurg Clin N Am, 1 (1990) 277. — 30. TAMARGO RJ, WALTER KA, OSHIRO EM, New Horiz, 5 (1997) 364. — 31. YEHUDA R, SOUTHWICK SM, GILLER EL, MA X, MASON J, J Nerv Ment Dis, 180 (1992) 321. — 32. SOUTHWICK SM, KRYSTAL JH, MORGAN A, JOHNSON D, NAGY ML, NICOLAU A, Arch Gen Psychiatry, 50 (1993) 266. — 33. SOUTHWICK SM, KRYSTAL JH, BREMNER D, MORGAN A, NICOLAU AL, NAGY LM, Ach Gen Psychiatry, 54 (1997) 749. — 34. DERACIOTI TD JR, BAKER DG, EKHATOR NN, WEST SA, HILL KK, BRUCE AB, SCHMIDT D, ROUNDS-KUGLER B, YEHUDA R, KECK PE JR, KASCKOW JW, Am J Psychiatry, 158 (2001) 1227. — 35. SOUTHWICK SM, BREMNER JD, RASMUSSON A, MORGAN CA 3RD, ARNSTEN A, CHARNEY DS, Biol Psychiatry, 46 (1999) 1192. — 36. YEHUDA R, LOWY MT, SOUTHWICK SM, SHAFFER S, GILLER EL, Am J Psychiatry, 149 (1991) 499. — 37. CHROUSOS GP, GOLD PW, JAMA, 267 (1992) 1244. — 38. KOSTEN TR, MASON JW, GILLER EL, OSTROFF RB, HARKNESS L, Psychoneuroendocrinology, 12 (1987) 13. — 39. O'DONNELL T, HEGADOREN KM, COUPLAND NC, Neuropsychobiology, 50 (2004) 273. — 40. PERVANIDOU P, CHROUSOS GP, Prog Brain Res, 182 (2010) 149. — 41. VIDELOCK EJ, PELEG T, SEGMAN R, YEHUDA R, PITMAN RK, SHALEV AY, Int J Neuropsychopharmacol, 11 (2008) 373. — 42. SHIOGAI I, KOSHIMURA M, MURATA Y, NOMURA H, DOI A, MAKINO M, Acta Neurochir, 86 (2003) 57. — 43. LISAK M, TRKANJEC Z, MIKULA I, DEMARIN V, Mt Sinai J Med, 72 (2005) 346. — 44. VINGERHOETS G, LUPPENS E, Neuropsychologia, 39 (2001) 1105. — 45. HARDERS AG, LABORDE G, DROSTE DW, RASTOGI E, Int J Neurosci, 47 (1989) 91. — 46. CHAI WN, SUN XC, LV FJ, WAN B, JIANG L, Acta Neurochir Suppl, 110 (2011) 225. — 47. SOLTER V, THALLER V, KARLOVIĆ D, CRNKOVIĆ D, Croat Med J, 43 (2002) 685.

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UTJECAJ POVIŠENE RAZINE KATEHOLAMINA U BOLESNIKA S KRONIČNIM POSTTRAUMATSKIM STRESNIM POREMEĆAJEM NA CEREBRALNU HEMODINAMIKU

SAŽETAK

Cilj ovog istraživanja je utvrditi povezanost između razine kateholamina i promjena cerebralne hemodinamike u bolesnika s kroničnim postraumatskim stresnim poremećajem (PTSP). Ispitivanjem je obuhvaćeno 50 bolesnika s kroničnim PTSP-em koji su prvi puta hospitalizirani i psihijatrijski liječeni te 50 zdravih ispitanika kontrolne skupine. Svi

ispitanici bili su u dobi između 30 i 50 godina. PTSP bolesnicima prvog su dana boravka analizirane vrijednosti vanilmandelične kiseline (VMA) i metabolita adrenalina i noradrenalina u 24-satnom urinu te je učinjena analiza krvnih žila Willisovog kruga transkranijskom dopler sonografijom (TCD). Isti dijagnostički postupci ponovljeni su nakon 21-dnevnog medikamentoznog psihijatrijskog tretmana. Prva analiza pokazala je istovremeno povišene razine 24-satne VMA kod 29 (58,00%) bolesnika i povišene vrijednosti srednjih brzina strujanja krvi (SBSK) krvnih žila Willisova kruga u 34 (68,00%) bolesnika što ukazuje na visoku podudarnost promatranih parametara (p=0,3290). Druga analiza koja je učinjena nakon 21-dnevnog psihijatrijskog liječenja pokazala je istovremeno povišenu razinu 24-satne VMA u 8 (16,00%) bolesnika i povišene SBSK krvnih žila Willisova kruga u 9 (18,00%) bolesnika što ukazuje na visoku podudarnost promatranih parametara (p=0,7906). U kontrolnoj skupini osoba bez PTSP-a svega je 2 (4,00%) ispitanika imalo povišene SBSK krvnih žila Willisova kruga, dok je razina 24-satne VMA u svih ispitanika bila uredna. Istraživanje je pokazalo značajnu povezanost između povišene razine stresnih hormona i povišenih SBSK u krvnim žilama Willisovog kruga koje su uzrokovane cerebralnim vazospazmom. Medikamentozno psihijatrijsko liječenje PTSP-a u trajanju od tri tjedna dovelo je do značajnog smanjenja udjela bolesnika s povišenom razinom metabolita kateholamina i značajnog smanjenja cerebralnog vazospazma. Rezultati istraživanja su pokazali visok stupanj korelacije između dnevne razine VMA i povišenih SBSK u krvnim žilama Willisovog kruga što jasno ukazuje da dugotrajno povišena razina kateholamina utječe na cerebralnu hemodinamiku.