University of Belgrade, School of Medicine, Belgrade[1]
Clinical Center of Serbia, Clinic of Neurology, Belgrade[2]
University of Belgrade, Faculty of Philosophy,
Department of Psychology, Belgrade[3]

AFFECTIVE STATUS IN CEREBRAL SMALL VESSEL DISEASE

AFEKTIVNI STATUS KOD BOLESTI MALIH KRVNIH SUDOVA MOZGA

**Aleksandar STEVANOVIĆ[1], Anja STEFANOVIĆ[3], Nataša STOJANOVSKI[1], Gordana TOMIĆ[2],
Jasna ZIDVERC TRAJKOVIĆ[1, 2] and Aleksandra M. PAVLOVIĆ[1, 2]**

Summary

Introduction. Cerebral small vessel disease is a neurological condition characterized by motor, cognitive and affective disorders, often found on brain magnetic resonance imaging scans in patients with vascular risk factors. Affective disorders may have a major impact on patients' quality of life, although they are often ignored as an entity in cerebrovascular pathology. **Material and Methods.** This prospective study included 80 patients with the diagnosis of cerebral small vessel disease admitted at the Clinic of Neurology, Clinical Center of Serbia in the period from January 1, 2017 to January 1, 2019. Baseline demographic data and brain magnetic resonance findings were obtained along with the results of cognitive function and affective status tests. Data were analyzed using standard statistical tests. **Results. S**tandard screening tests revealed that 51.25% and 33.75% of our patients with cerebral small vessel disease suffer from apathy and depression, respectively. A significant correlation was found between the severity of white matter changes on magnetic resonance scans and apathy (p = 0.0092). Additionally, white matter changes were also significantly associated with depression (p = 0.021). **Conclusion.** Affective disorders are not uncommon in cerebral small vessel disease and apathy was the leading phenomenon among our patients. Since a strong correlation was detected between affective disorders and severity of vascular changes on magnetic resonance scans, we may conclude that both apathy and depression are key features of an underlying brain injury, rather than just comorbidity.

Keywords: Cerebral Small Vessel Diseases; Affective Symptoms; Mood Disorders; Apathy; Depression; Cognition; Magnetic Resonance Imaging; Stroke, Lacunar

Sažetak

Uvod. Bolest malih krvnih sudova mozga je neurološko stanje za koje su karakteristični motorni, kognitivni i afektivni poremećaji i koje se često dijagnostikuje na snimcima mozga magnetnom rezonancijom kod pacijenata sa vaskularnim faktorima rizika. Promene u afektivnom statusu imaju veliki uticaj na kvalitet života pacijenata iako su neretko bile zanemaren fenomen u cerebrovaskularnoj patologiji. **Materijal i metode.** U prospektivnoj studiji obuhvaćeno je 80 pacijenata sa dijagnozom bolest malih krvnih sudova mozga lečenih i ispitivanih na Klinici za neurologiju Kliničkog centra Srbije, u periodu od 1. januara 2017. godine do 1. januara 2019. godine. Analizirani su osnovni demografski podaci, nalaz na magnetnoj rezonanciji mozga i rezultati testova kognitivnih funkcija i afektivnog statusa, upotrebom standardnih statističkih metoda. **Rezultati.** Rezultati testova za apatiju i depresiju ukazali su da je 51,25% bolesnika sa ovom bolešću pokazivalo prisustvo apatije, a 33,75% prisustvo depresivnog poremećaja. Dokazana je statistički značajna povezanost između težine lezija bele mase mozga na magnetnorezonantnim snimcima mozga i apatije (p = 0,0092), odnosno težine lezija bele mase i depresije (p = 0,021). **Zaključak.** Izmene afektivnog statusa nisu retka manifestacija cerebralne bolesti malih krvnih sudova mozga, a najčešći fenomen u našoj grupi bolesnika bila je apatija. Budući da je detektovana značajna povezanost između afektivnih poremaćaja i težine vaskularnih lezija na magnetno-rezonantnim snimcima mozga, smatramo da su apatija i depresivnost najpre deo kliničke slike ove bolesti a ne jedan od komorbiditeta.

Ključne reči: bolest malih krvnih sudova; afektivni simptomi; poremećaji raspoloženja; apatija; depresija; kognicija; magnetna rezonanca; lakunarni moždani udar

Introduction

Cerebral small vessel disease (CSVD) is a progressive vascular disease affecting small perforating arteries, arterioles, capillaries and venules of the brain, characterized by typical clinical and neuroimaging findings [1]. Magnetic resonance imaging (MRI) of the brain shows lacunar infarctions, white-matter hyperintensities (WMH) and cerebral microbleeds along with cortical atrophy and enlargement of perivascular spaces [2]. Development and progression of CSVD is associated with common vascular risk factors, leading to the highest prevalence of CSVD among elderly patients [3]. Besides motor (pyramidal and extrapyramidal signs, gait difficulties) and sensory manifestations, clinical presentation of CSVD also includes loss of sphincter control and changes in cognitive function and affective status.

Cognitive decline in CSVD varies from mild vascular-cognitive impairment (VCI) to overt vascular

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Corresponding Author: Doc. dr Aleksandra M. Pavlović, Klinički centar Srbije, Klinika za neurologiju,
11000 Beograd, Dr Subotića 6, E-mail: aleksandra3003@yahoo.com

dementia with main affection of frontal and subcortical cerebral areas [1]. Changes in affective status, including depression and apathy, are not uncommon but are likely underdiagnosed and undertreated [1]. It can be challenging to differentiate depression and apathy as they share many overlapping symptoms. Apathy is characterized by the loss of motivation, pathological indifference and absence of common emotional reactions, but on the other hand, loss of motivation is also one of the major symptoms of depression [4, 5]. Also, patients are at an increased risk of depressive episode after an ischemic stroke of any type, and 20 – 25% of all strokes are due to CSVD. Both apathy and depression are associated with a decline in quality of life, failure of the rehabilitation process and an increased risk of cognitive impairment [1, 5, 6].

Full neuropsychological and psychiatric assessment of patients with CSVD is time-consuming and expensive, but bedside screening tests may fail to differentiate apathy from depression. It is possible to overestimate the presence of depression in patients with CSVD, and at same time underestimate the number of cases with apathy. This difference could be clinically significant, because common depression treatment strategies may not target symptoms of apathy [7]. The aim of this study was to analyze affective status in a cohort of inpatients treated for symptomatic CSVD using standard screening tests.

Material and Methods

This prospective study was approved by the Ethics Committee of the Clinical Center of Serbia and included 80 patients with clinical an MR diagnosis of CSVD, admitted to the Clinic of Neurology, University of Belgrade, in the period January 1, 2017 - January 1, 2019. Baseline demographic data, risk factors and clinical presentations were collected from medical records, and all participants underwent cognitive function and affective status testing as well as standard MR scanning. All patients were diagnosed with CSVD, based on medical history, neurological examination, MR findings and results of additional tests used to exclude similar neurological conditions.

Patients included in this study completed standardized screening questionnaires on their symptoms of depression, apathy and anxiety [8–10]. Patients were asked to fill out two more questionnaires concerning

their quality of life and presence of major stressful life events [11, 12]. All patients were tested for their cognitive status using standardized methods [13].

The presence and severity of depression symptoms was evaluated by the second revision of Beck Depression Inventory (BDI-II) test. This self-report inventory consists of 21 multiple-choice questions with a maximum total score of 63 points. Patients with a total score of 14 points or more, were classified as positive for symptoms of depression, while those with a total score less than 14 points were classified as depression free [10]. The presence and severity of apathy symptoms was evaluated by using a modified version of Apathy Evaluation Scale (AES). This self-report inventory consists of 14 multiple-choice questions with a maximum total score of 42 points. Patients with a total score of 14 points or more were classified as apathy-positive group, while those with a total score less than 14 points were classified as apathy-free [8]. The presence and severity of anxiety symptoms was evaluated by Beck Anxiety Inventory (BAI). This self-report inventory consists of 21 multiple-choice questions with a maximum total score of 63 points. Patients with a total score of 22 points or more were classified as anxiety-positive, while those with a total score of 21 points or less were classified as anxiety-free [9].

The quality of life was assessed using the Serbian translation of a 36-Item Short Form Health Survey (SF-36), taking into consideration only the total scores [11]. Experience of stressful life events was registered with the Holmes-Rahe Stress Inventory (HRSI). This self-report inventory consists of 43 different major stressful life events. Patients were asked to identify if such events happened within the last year. According to the total result, we made two groups of patients: experiencing mild stress (150 points or less) and experiencing excessive level of stress (150 points or more) [12].

Mini-Mental State Examination (MMSE) test was used for the detection and measurement of cognitive impairment. Patients with a total score of 24 points or more were classified as patients with normal cognition, while those with a total score less than 24 points were classified as cognitively impaired [13].

The analysis included baseline demographic data on sex and age, as well as results of neuropsychological tests and MR lesion severity. Brain MR findings were analyzed for the presence of lacunar infarctions, white matter hyperintensities (WMH) and Age-Related White Matter Changes Scale (ARWMC) and Fazekas scale. The ARWMC scale illustrates overall cerebral damage with WMH and lacunar infarctions, with a range from 0 (no damage) to 30 (maximal damage) [14]. Fazekas scale is used to quantify the amount of WMHs seen on brain MR scans. All brain MR scans are given a grade ranging from 0 (absent lesions) to grade 4 (large confluent areas), with separate scoring for periventricular (PV) and subcortical (SC) lesions [15].

All neuropsychological testing and MR grading were performed by trained examiners blinded for clinical data. Data were processed using IBM SPSS 23 program (IBM, New York, USA). We used de-

scriptive and analytical statistical methods. Numerical variables were calculated in terms of arithmetic mean and standard deviation. To determine a significant difference and/or correlation between the parameters, Chi-squared test and Spearman test of correlation were used. The $p < 0,05$ was considered statistically significant.

Results

Demographic data
Our study included a total of 80 participants diagnosed with CSVD, 58 (72.5%) female and 22 (27.5%) male patients, mean age of 56.3 ± 15.0 years, ranging from 23 to 81 years.

Affective status
Results of neuropsychological testing are shown in **Table 1**. Symptoms of apathy were recorded in more than half of our patients (41 patients or 51.25%). One third (27 or 33.75%) of patients reported symptoms of depression. Symptoms of anxiety were less common, present only in 12 patients (15%) **(Table 1)**.

Brain MR findings
Brain MR findings are summarized in **Table 2**. MR detected lacunar infarctions in all participants (100.0%), while presence of WHM was less frequent (37.5%). The mean value of ARWMC score was relatively low (8.25, median 6). Fazekas grading scales indicated presence of typical PV lesions in 27 (33.75%) patients, while SC lesions were present in 79 (98.75%) patients. The mean value of both PV and SC WMH scores on Fazekas scale was 1 (mild lesions).

Correlation between neuropsychological scores and demographic data
Male patients (77.3%) reported symptoms of apathy more often than female participants (41.4%, p = 0.0056), and also had higher total scores on corresponding inventory (mean score 16.8 in men and 12.6 in women; p = 0.011) **(Table 3)**.
No significant difference was found between the sexes regarding depressive symptoms (40.91% in males and 31.03% in female patients; p = 0.426). The same findings were detected for symptoms of anxiety (18.18% in male and 13.79% in female patients; p = 0.750). The mean scores on applied tests also did not differ between sexes **(Table 3)**.

Correlation between affective status and cognitive changes
A significant correlation was found between presence of apathy and VCI (r = 0.309, p = 0.00528). No such correlation was found in case of anxiety (r = -0.0737, p = 0.518) but it was at the level of statistical trend for depression (r = 0.206, p = 0.067).

Correlation of affective status and quality of life
Presence of apathy (r = -0.448, p < 0.001), depression (r = -0.410, p = 0.001) as well as anxiety (r =

Table 1. Frequency of affective disorders and mean scores on screening inventories in patients with CSVD
Tabela 1. *Učestalost afektivnih poremećaja i srednje vrednosti rezultata skrining testova u grupi ispitanika sa BMKS*

	Screening outcome/*Ishod skrininga*	N/*Broj*	%	x̄+SD
Depression/*Depresija*	Present/*Prisutna*	27	33.75	21.00 + 7.19
	Not present/*Nije prisutna*	53	66.25	4.47 ± 3.50
Anxiety/*Anskioznost*	Present/*Prisutna*	12	15.0	32.08 ± 4.79
	Not present/*Nije prisutna*	68	85.0	8.63 ± 5.27
Apathy/*Apatija*	Present/*Prisutna*	41	51.25	18.66 + 4.42
	Not present/*Nije prisutna*	39	48.75	8.62 + 3.11

Legenda: BMKS – bolest malih krvnih sudova

Table 2. Severity of vascular lesions detected on brain MR
***Tabela 2.*** *Težina vaskularnih lezija na magnetno-rezonantnim snimcima mozga*

	Number of patients/*Broj pacijenata* (%) x̄ + SD
Lacunar infarctions, n (%)/*Lakunarni infarkti*	80 (100.0)
WMH/HBM, n (%)	30 (37.5)
ARWMC, x̄ + SD (median)	8.25 + 5.17 (6.0)
Fazekas PV, x̄ ± SD (mod)	0.76+ 1.13 (0)
Fazekas SC, x̄ ± SD (mod)	1.39 + 0.61 (1)

Legend: WMH - white matter hyperintensities, ARWMC - Age Related White Matter Changes, PV periventricular, SC - subcortical, ARWMC – Age Related White Matter Changes score
Legenda: HBM – hiperinziteti bele mase, PV – periventrikularno, SC – supkortikalno, ARWMC – skor lezija bele moždane mase u vezi sa starošću

Table 3. Achievements on screening inventories between sexes
Tabela 3. *Razlike u rezultatima skrining testova među polovima*

	Female/*Žene*	Male/*Muškarci*	p/*p*
Depression, x̄+SD/*Depresija*	9.53 + 9.53	11.41+8.86	0.426
Anxiety, x̄±SD/*Anksioznost*	11.93 + 10.18	12.73 + 9.28	0.750
Apathy, x̄+SD/*Apatija*	12.62 + 6.01	16.77 + 6.28	0.011
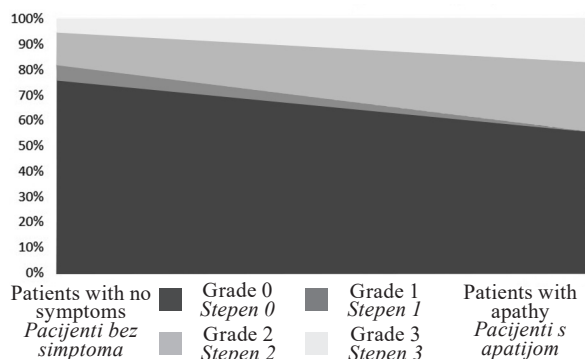
Graph 1. Correlation of periventricular white-matter lesions expressed in Fazekas grading scale and presence of apathy in patients with CSVD
Grafikon 1. *Povezanost periventrikularnih lezija bele mase izraženih u Fazekas gradusima i prisustva apatije kod pacijenata sa bolestima malih krvnih sudova mozga*
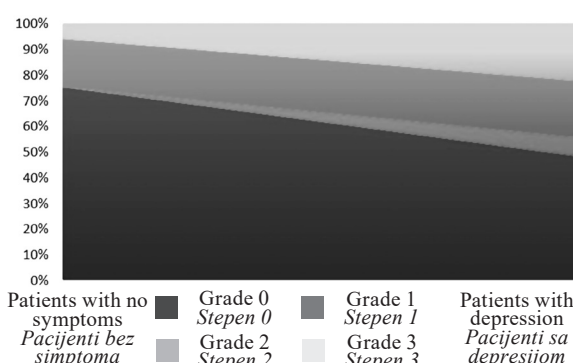

Graph 2. Correlation of periventricular white-matter lesions expressed in Fazekas grading scale and presence of depression in patients with CSVD
Grafikon 2. *Povezanost periventriknlarnih lezija bele mase izraženih u Fazekas gradnsima i prisustva depresije kod pacijenata sa BMKS mozga*

-0.378, p = 0.002) in our patients was associated with lower quality of life according to total scores on SF-36 inventory.

Correlation of affective status and major stressful life events

No significant correlation was found between reporting major stressful life events and outcomes on depression and anxiety inventories (p for both > 0.1), but it approached statistical significance for apathy (r = 0.205, p = 0.091).

Correlation between affective and cognitive status and brain magnetic resonance imaging findings

A significant correlation was found between ARWMC scores and results on BDI (p = 0.0092). There was also a significant correlation between ARWMC scores and results on AES (p = 0.021). On the other

hand, no correlation was found between ARWMC scores and results on BAI (p = 0.368) **(Table 4)**.

The strongest association was found between PV scores on Fazekas scale and presence of apathy (p = 0.048) as well as depression symptoms (p = 0,015; **Graphs 1** and **2**). Other correlations were negative, except for the apathy symptoms and Fazekas SC scores, which approached statistical significance (p = 0.081).

A statistically strong association was found for performance on cognitive test (MMSE) and Fazekas PV and SC scores, respectively (p < 0.001).

Discussion

Our study results indicate that changes in affective status are not uncommon in patients with CSVD, surprisingly leading with apathy symptoms. More

Table 4. Relationship between affective symptoms and severity of vascular lesions on MR
Tabela 4. *Odnos afektivnog statusa i težine vaskulamih lezija mozga na magnetno-rezonantnim snimcima*

	Screening outcome/*Ishod testa*	ARWMC score, x̄ + SD/*ARWMC skor,* x̄ ± SD	p/*p*
Depression/*Depresija*	Present/*Prisutna*	10.33 + 6.09	0.0092
	Not present/*Nije prisutna*	7.19 + 4.32	
Anxiety/*Anksioznost*	Present/*Prisutna*	9.50 + 5.30	0.368
	Not present/*Nije prisutna*	8.03 + 5.16	
Apathy/*Apatija*	Present/*Prisutna*	9.54 + 5.84	0.021
	Not present/*Nije prisutna*	6.89 + 4.00	

Legend: ARWMC – Age Related White Matter Changes score
Legenda: ARWMC – skor lezija bele moždane mase u vezi sa starošću

than a half of patients included in this study (51.25%) reported symptoms of apathy, while depression, typically recognized as a CSVD manifestation, was leading with 33.75%. Current research on affective status in patients with CSVD also came to similar conclusions, revealing that in some cohorts of patients apathy was the leading symptom in early-stage disease [5, 7].

Both apathy and depression were associated with cognitive decline and decrease in quality of life of patients with CSVD, especially in those with dysexecutive syndrome which is one of the major manifestations of the disease [4, 5]. Our study results are in accordance with this finding, showing a significant change in affective status as well as cognitive impairment and a decline in quality of life.

In accordance to Alexopoulos vascular depression hypothesis, underlying pathological mechanism could be a syndrome of disconnection due to vascular white matter lesions which affect frontolimbic and frontostriatal networks [15, 16]. Results of self-report screening inventories for apathy and depression have shown excellent correlation with vascular lesions predominantly in white matter, quantified by ARWMC and Fazekas scales. The research of Hollock et al. reported that a more intense association exists between white matter lesions and apathy due to disruption of cortico-subcortical pathways [5, 7]. Symptoms of apathy are linked to lesions of limbic associative pathways such as anterior cingulate cortex, fornix and fasciculus uncinatus [5, 15]. Furthermore, presence of depression relates to higher ARWMC scores. However, it is a composite score, so exact localization of the lesions was not analyzed in our study. In accordance to current research, our study results reveal significant association between PV lesions and changes in affective status, whereas SC lesions were more frequently linked to cognitive decline [5, 15].

These findings are valuable because they could enable early identification of patient neuroradiological profile thus creating different clinical subgroups more susceptible to cognitive and/or affective decline etc.

We present data from well-defined cohort of patients with CSVD who underwent comprehensive clinical, neuropsychological and neuroimaging assessment. Limitations of our study are related to nature of self-report testing, a method available only to patients with mild motor and/or cognitive impairment, and therefore more severely affected patients were not included in the study. Nevertheless, these short screening inventories are very accessible, so their use in everyday practice is simple, affordable and achievable in hospital conditions for early detection on affective status decline. Also, our study has not considered the impact of different therapeutics frequently used in patients with neuropsychiatric disorders such as antidepressants and tranquilizers, which could possibly interfere with the results [16]. Since vascular depression and apathy are often resistant to available pharmacotherapy, prevention of vascular lesions which could be the underlying cause of these phenomena and further research on new therapeutic strategies is of utmost importance [17].

Conclusion

Results of our study indicate that changes in affective status are not uncommon in patients with cerebral small vessel disease. These changes correlate with cognitive decline and severity of vascular lesions detected on brain magnetic resonance imaging. Since these changes are undoubtedly linked to decrease in quality of life, early recognition of these phenomena is of utmost importance for selecting the best therapeutic strategies.

References

1. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010;9(7):689-701.

2. Pantoni L. Pathophysiology of age-related cerebral white matter changes. Cerebrovasc Dis. 2002;13(Suppl 2):7-10.

3. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. Lancet Neurol. 2013;12(5):483-97.

4. Lohner V, Brookes RL, Hollocks MJ, Morris RG, Markus HS. Apathy, but not depression, is associated with executive dysfunction in cerebral small vessel disease. PLoS One. 2017;12(5): e0176943.

5. Hollocks MJ, Lawrence AJ, Brookes RL, Barrick TR, Morris RG, Husain M, et al. Differential relationships between apathy and depression with white matter microstructural changes and functional outcomes. Brain. 2015;138(Pt 12):3803-15.

6. Moran C, Phan TG, Srikanth VK. Cerebral small vessel disease: a review of clinical, radiological, and histopathological phenotypes. Int J Stroke. 2011;7(1):36-46.

7. Tay J, Tuladhar AM, Hollocks MJ, Brookes RL, Tozer DJ, Barrick TR, et al. Apathy is associated with large-scale white matter network disruption in small vessel disease. Neurology. 2019;92(11):e1157-67.

8. Serrano-Dueñas M, Martínez-Martín P, Merchán T, Bravo R, Serrano M. Properties of the Apathy Scale (AS) for use on Parkinson's patients. Advances in Parkinson's Disease. 2013;2(2):53-7.

9. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988;56(6):893-7.

10. Beck AT, Steer RA, Ball R, Ranieri WF. Comparison of Beck Depression Inventories-IA and -II in psychiatric outpatients. J Pers Assess. 1996;67(3):588-97.

11. Pekmezović T, Ječmenica-Lukić M, Petrović I, Špica V, Tomić A, Kostić VS. Quality of life in patients with progressive supranuclear palsy: one-year follow-up. J Neurol. 2015; 262(9):2042-8.

12. Noone PA. The Holmes–Rahe Stress Inventory. Occup Med. 2017;67(7):581-2.

13. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc. 1992;40 (9):922-35.

14. Fazekas F, Barkhof F, Wahlund L, Pantoni LO, Erkinjuntti T, Scheltens P, et al. CT and MRI rating of white matter lesions. Cerebrovasc Dis. 2002;13(Suppl 2):31-6.

15. Pavlovic AM, Pekmezovic T, Zidverc Trajkovic J, Svabic Medjedovic T, Veselinovic N, Radojicic A, et al. Baseline char-

acteristic of patients presenting with lacunar stroke and cerebral small vessel disease may predict future development of depression. Int J Geriatr Psychiatry. 2015;31(1):58-65.

16. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use. CNS Drugs. 2004;18(1):37-48.

17. Laird KT, Krause B, Funes C, Lavretsky H. Psychobiological factors of resilience and depression in late life. Transl Psychiatry. 2019;9(1):88.