Research Article

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Suffering from cerebral small vessel disease with and without metabolic syndrome

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Abstract: Background: Cerebral small vessel disease (CSVD) and metabolic syndrome were separately associated with cognitive impairment and depression. However, whether metabolic syndrome adds to cognitive impairment and depression in patients who already have CSVD remained unanswered.

Objective: The aim of our study was to investigate the association of metabolic syndrome with cognitive impairment and depression in patients with CSVD who have lacunar lesions or white matter hyperintensities.

Methods: This prospective cohort study was conducted at Neurology Clinic, Clinical Center, Kragujevac, Serbia. Main outcomes of the study were cognitive assessment, and assessment of depression among hospitalized patients with or without CSVD.

Results: The study included 74 inpatients, 25 of them having lacunary infarctions, 24 with the white matter hyperintensities, and 25 control patients without CSVD. The CSVD was accompanied by impairment of cognition and depression, the patients with lacunary lesions being more cognitively impaired and more depressive than the patients with the white matter hyperintensities. The patients with CSVD who also had metabolic syndrome were more cognitively impaired and depressed than the patients with CSVD alone.

Conclusions: In conclusion, our study showed that metabolic syndrome is associated with further worsening of already impaired cognition and existing depression in patients with CSVD.

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1 Introduction

Cerebral small vessel disease (CSVD) could be defined as a set of signs, symptoms and changes in the brain morphology that is caused by damage of perforating cerebral arterioles, capillaries or venules [1]. Although some patients with CSVD have so-called "silent" brain lesions, almost 45% will eventually develop dementia, and a variety of neurological symptoms could also be expected. The most frequent findings on brain imaging are subcortical lacunar lesions and white matter hyperintensities, while small bleedings, widened perivascular spaces and brain atrophy could also be seen [2]. Prevalence of the CSVD in persons older than 50 years is rather high, and a recent study found that among the stroke-free neurological patients 14.5% had lacunary lesions, 65.4% deep white matter hyperintensity, and 10.6% cerebral microbleeds [3].

Metabolic syndrome, defined as co-occurrence of insulin resistance (and/or glucose intolerance), obesity, hypertension and dyslipidemia with atherogenic potential [4], was associated with lacunar lesions, but not with progression of white matter hyperintensities in some studies [5]. It was shown that the use of lipid-lowering drugs decreases incidence of lacunar lesions [6], and hypertension was proven as an independent risk factor for emergence of the CSVD [7]. The CSVD was strongly associated with cognitive impairment and depression [8], as well as type 2 diabetes mellitus with cognitive impairment [9]. Although a majority of previous studies involving CSVD focused on motor impairment and mortality, cognitive decline also contributes to overall functional impairment of the patients, further decreasing their capability to perform usual activities of daily living and making them more dependent on the others [10]; it was recently shown that depression is the most important predictor of poor functional outcome in patients with CSVD [11]. However,

whether metabolic syndrome adds to cognitive impairment and depression in patients who already have CSVD remained unanswered in current medical literature.

The aim of our study was to investigate the association of metabolic syndrome with cognitive impairment and depression in patients with CSVD who have lacunar lesions or white matter hyperintensities.

2 Methods

This prospective cohort study was conducted at Neurology Clinic, Clinical Center, Kragujevac, Serbia, a tertiary care, government-funded hospital, from February the 1st, 2017 to December the 31st, 2017. The inclusion criteria for the study were as the following: age over 18 years, initial admittance to the Intensive Care Unit (ICU) of the Neurology Clinic, hospitalized for more than 30 days and examined by the Nuclear Magnetic Resonance (NMR) head scan for signs of CSVD. The patients were excluded if they had diabetes mellitus, were taking medication that may influence congnition or mood, had a hereditary and acquired disorders of hemostasis, had a systemic diseases of connective tissue and if the protocol was violated. The study sample was consecutive, i.e. all patients who satisfied inclusion, and did not have exclusion criteria within the study period were enrolled. Main outcomes of the study were assessment of cognition and depression among the study patients. The study was approved by the Ethics Committee of Clinical Center, Kragujevac, and conducted according to the Good Clinical Practice and Declaration of Helsinki about experimentation on human subjects. The patients signed the informed consent form prior to the enrollment.

Heart rate, systolic and diastolic blood pressure, body temperature, weight, height and waist circumference were measured on admission to the hospital. On the 2nd – 7th day of hospitalization the NMR head scan was made, serum lipoproteins, uric acid, C-reactive protein, glucose and insulin levels were measured, and oral glucose tolerance test was performed. Montreal Cognitive Assessment (MoCA) [12] and Beck's Depression Inventory (BDI) [13] were used to estimate cognition and mood on the 30th day of the current hospitalization. The MoCA is 30-point test specifically designed to detect vascular cognitive impairment, which needs 30 minutes to be administered. It makes assessment of the following domains of cognition: the short-term memory, visuospatial ability, attention, concentration, and working memory, orientation in time and place, language, phonemic fluency, and verbal abstraction. The BDI is a 21-question self-administered scale for assessment of depression severity. There are three domains of depression assessed by the BDI: cognitive-affective, performance, and somatic symptoms. It is used to assess depression in a variety of settings, including outpatients and inpatients. A patient score on the BDI may range from 0 (no depression) to 63 (the most severe depression).

Type of the data distribution was tested by the Shapiro-Wilks test, and non-parametric statistical tests were used for comparisons if the normality was not confirmed. Continuous variables were described by median and range, and categoric ones by rates and percentages. Significance of differences in values of continuous variables between the study groups (defined according to the presence and type of the brain lesions) was tested by the Kruskal-Wallis analysis of variance, with post-hoc pairwise comparisons using the Mann-Whitney U test. The differences in rates of categorical variables were tested by the Chi-square test. Influences of the study variables on the BDI and the MoCA scores achieved by the patients were investigated by multivariate linear regression. The differences were considered significant if probability of zero-hypothesis was less than 0.05. All calculations were performed by the Statistical Program for Social Sciences (SPSS), version 18.

3 Results

The study included 74 inpatients, 25 of them having lacunary infarctions, 24 with white matter hyperintensities, and 25 control patients without CSVD, as confirmed by Nuclear Magnetic Resonance imaging of the brain on 2nd – 7th day of hospitalization. The patients from the control group were admitted to the ICU due to head injury without brain damage (8 pts), status epilepticus (11 pts), herniated intervertebral disc with functional deficit (5 pts) and Guillain-Barre syndrome (2 pts). Characteristics of the study groups are shown in Table 1.

On the 30th day of hospitalization the study patients were tested by the Montreal Cognitive Assessment: median scores (with range in parenthesis) were 19.0 (15.0 – 23.0), 21.0 (18.0 – 27.0) and 26.0 (21.0 – 30.0), achieved by the patients with lacunary infarctions, with the white matter hyperintensities and by the control patients, respectively. The difference between the groups was significant according to the Kruskal-Wallis analysis of variance ($p = 0.000$), and pairwise comparisons between the groups by the

Table 1. Characteristics of the study sample, divided according to the type of brain ischemic lesions. Being not normally distributed, values of the continuous variables are presented as median with range, while values of categorical variables are shown as rates and percentages. Significance of difference among the study groups in values of continuous variables was tested by Kruskal-Wallis nonparametric analysis of variance, while the categorical variables were compared by Chi-square test.

Variable	Patients with lacunary infarctions (n=25)	Patients with the white matter hyperintensities (n=24)	Control patients (n=25)	p-value
Age (years)	72.0 (66.0 – 79.0)	70.5 (64.0 – 77.0)	60.0 (33.0 – 70.0)	0.000*
Sex (male/total)	11/25 (44%)	12/24 (50%)	13/25 (52%)	0.887
Heart rate on admission (bpm)	68 (60 – 88)	71.5 (60 – 89)	65 (47 – 83)	0.010*
Systolic blood pressure on admission (mmHg)	140 (120 – 167)	147 (132 – 172)	134 (120 – 153)	0.001*
Diastolic blood pressure on admission (mmHg)	90 (65 – 110)	87.5 (68 – 105)	80 (66 – 95)	0.115
Body temperature on admission (oC)	36.3 (36 – 37.3)	36.3 (36 – 36.8)	36.4 (35.9 – 36.7)	0.475
Patients with sinus rhythm/total	19/25 (76%)	16/24 (67%)	21/25 (84%)	0.368
Serum level of glucose on 2nd – 7th day (mM)	5.9 (4.8 – 7.1)	5.8 (4.8 – 6.3)	5.8 (4.8 – 7.2)	0.550
Serum level of carbamide on 2nd – 7th day (mM)	8.7 (6.7 – 12.0)	7.7 (5.2 – 11.1)	6.3 (4.3 – 10.1)	0.000*
Serum level of creatinine on 2nd – 7th day (mM)	83.0 (63.0 – 100.0)	88.0 (70.0 – 110.0)	69.0 (45.0 – 90.0)	0.000*
C-reactive protein in serum on 2nd – 7th day (mg/L)	16.2 (4.5 – 95.7)	15.0 (4.4 – 25.6)	7.8 (4.0 – 16.9)	0.000*
Serum level of uric acid on 2nd – 7th day (mM)	269.0 (132.0 – 658.0)	365.0 (112.0 – 589.0)	256.0 (123.0 – 546.0)	0.084
Red cell count on 2nd – 7th day (x 1012/L)	4.25 (3.12 – 4.97)	4.36 (3.56 – 4.89)	4.56 (3.88 – 4.98)	0.079
White cell count on 2nd – 7th day (x 109/L)	6.9 (4.8 – 14.6)	7.2 (4.5 – 13.1)	6.9 (4.7 – 9.8)	0.269
Platelet count on 2nd – 7th day (x 109/L)	278.0 (189.0 – 369.0)	280.5 (196.0 – 385.0)	358.0 (178.0 – 456.0)	0.009*

* significant difference

Mann-Whitney test showed that all groups were significantly different from each other (p = 0.000) (Figure 1).

The study patients were also tested by the Beck's Depression Inventory on the 30th day of hospitalization: median scores (with range in parenthesis) were 39.0 (6.0 – 54.0), 27.0 (3.0 – 47.0) and 9.0 (3.0 – 33.0), achieved by the patients with lacunary infarctions, with the white matter hyperintensities and by the control patients, respectively. The difference between the groups was significant according to the Kruskal-Wallis analysis of variance (p = 0.000), and pairwise comparisons between the groups by the Mann-Whitney test showed that all groups were significantly different from each other (p = 0.018) (Figure 2).

Presence of metabolic syndrome among the study patients was tested on the 2nd – 7th day of hospitalization. It was present in 17 patients with lacunary infarctions (68%), in 11 patients with the white matter hyperintensities (46%), and in 9 patients from control group (36%). However, the difference in rates of metabolic syndrome among the study groups was not significant (p = 0.054).

Metabolic syndrome in patients with CSVD was accompanied with higher score on Beck's Depression Inventory: the patients with metabolic syndrome achieved median score of 39.0 (21.0 – 54.0), and those without the metabolic syndrome 15.0 (3.0 – 33.0). The difference in scores was highly significant according to the Mann-Whitney U test (p = 0.000). On the contrary, the scores on the Montreal Cognitive Assessment were significantly lower in the CSVD patients with metabolic syndrome than in those without: 19.0 (15.0 – 21.0) vs. 21.0 (19.0 – 27.0), respectively (p = 0.000).

When the Montreal Cognitive Assessment score was chosen for the outcome variable in multivariate linear regression, the model constructed with backward deletion included five variables (presence and type of the ischemic brain lesions, metabolic syndrome, C-reactive protein level in serum, presence of sinus rhythm and the BDI score) and

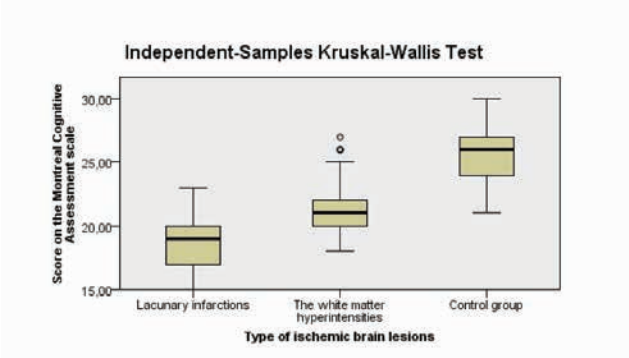

Figure 1. Median scores on the Montreal Cognitive Assessment scale with interquartile range achieved by patients with various types of ischemic brain lesions on the 30th day of hospitalization.

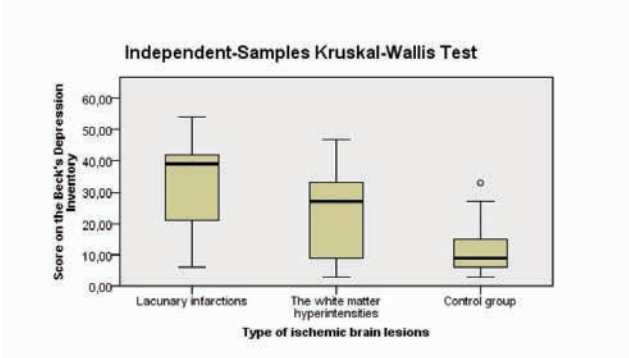

Figure 2. Median scores on the Beck's Depression Inventory with interquartile range achieved by patients with various types of ischemic brain lesions on the 30th day of hospitalization.

showed very good fit: the adjusted R square was 0.781. Significant influence on the MoCA score was demonstrated for presence and type of ischemic brain lesions (B coefficient 2.283 [95% confidence interval from 1.657 to 2.909], p = 0.000), metabolic syndrome (B coefficient - 1.111 [95% confidence interval from - 0.171 to - 2.051], p = 0.021), sinus rhythm (B coefficient 1.093 [95% confidence interval from 0.147 to 2.049], p = 0.024), C-reactive protein in serum (B coefficient 0.041 [95% confidence interval from 0.002 to 0.079], p = 0.038) and BDI score (B coefficient - 0.105 [95% confidence interval from - 0.064 to - 0.145], p = 0.000).

When the Beck's Depression Inventory score was chosen for the outcome variable in multivariate linear regression, the model constructed with backward deletion included four variables (white cell count, systolic blood pressure, presence of sinus rhythm and Montreal Cognitive Assesssment score) and showed satisfactory fit: the adjusted R square was 0.678. Significant influence on the Beck's Depression Inventory score was demonstrated for sinus rhythm (B coefficient 7.572 [95% confidence interval from 3.046 to 12.097], p = 0.001), systolic blood pressure (B coefficient 0.186 [95% confidence interval from 0.016 to 0.355], p = 0.032), white cell count (B coefficient 1.366 [95% confidence interval from 0.349 to 2.383], p = 0.009) and the Montreal Cognitive Assessment score (B coefficient - 2.791 [95% confidence interval from - 2.196 to - 3.387], p = 0.000).

4 Discussion

Our study showed that CSVD was accompanied by the impairment of cognition and depression, the patients with lacunary lesions being more cognitively impaired and more depressive than the patients with the white matter hyperintensities. The patients with the CSVD who also had metabolic syndrome were further more cognitively impaired and depressive than the patients with the CSVD, but free from metabolic syndrome. The multivariate analysis confirmed that metabolic syndrome, when present in a patient with the CSVD, further decreases the MoCA score for 1.11 points.

The exact mechanisms on how metabolic syndrome may contribute to cognitive impairment are still unknown, but available evidence points that it causes damage of capillaries and small arterioles, with consequent injury of white matter and loss of previously established connections in brain cortex [14]. Hypertension and hyperlipoproteinemia within the framework of the metabolic syndrome increase vascular permeability and cause protein extravasation, further compromising oxygenation and nutrition of neurons. Insulin resistance may impair cerebrovascular reactivity, which also could hypothetically contribute to cognitive deficit. These processes are more intense in the presence of oxydative stress [15] or inflammation [14]; however, in our study increased C-reactive protein levels were not associated with decreased cognition. The patients with CSVD have already compromised microcirculation in the brain, characterised by widened perivascular space loaded with waste proteins [16], but whether and how it may be related to cognitive decline remains to be established in future studies. For the time being, and based on the results of our study, we could only claim that patients having both the CSVD and metabolic syndrome show more severe cognitive impairment and depressive symptoms than those having only CSVD, or controls, when measured on the 30th day of hospitalization.

Association of depression and metabolic syndrome was demonstrated in many studies, and there is certain evidence that initial step is induction of chronic inflammation by metabolic syndrome through neuropathy, impairment of the immune system, and disfunction of

platelets and endothelium [17]. Free oxygen and nitrogen radicals and cytokines released during the inflammation cause damage of microcirculation in the brain, leading to eventual death of neurons and disturbance of numerous higher cerebral functions, including mood disorders. Indeed, in our study each additional thousand of white cells per cubic millimeter increased score of the BDI reached by a CSVD patient for 1.3 points, and each additional mmHg of systolic blood pressure bore 0.19 points on the same scale. Since the CSVD was also noted to cause or worsen depression in other studies [18], it is not surprising that in our study the two factors acted synergistically, and the patients with both the CSVD and metabolic syndrome were more depressed than the patients with only CSVD.

Our results about effects of metabolic syndrome and CSVD to cognition and depression separately should be taken with reserve, because there is possibility of overlaping symptoms between cognitive impairment and depression. Severely depressed patients may score worse on scales for cognitive assessment including the MoCA due to reversible cognitive impaitment [19], giving false picture of pseudodementia. On the other hand, certain degree of cognitive impairment may bias assessment of depressive symptoms, including that made by the BDI, through hindering the capacity of understanding the questions properly and of correct recollection of memories for the answers, or just simply not being able to concentrate long enough for a task [20]. The study of Majer et al [21] further underlined neccessity to be cautious when interpreting changes in cognition and mood of patients with metabolic syndrome and CSVD, as it demonstrated that worse cognitive functions in patients with dementia were related to higher frequency and greater severity of symptoms related to depression, like apathy, irritability, sleep-wake cycle dysfunctions and changes of appetite.

Metabolic syndrome additionally contributes to development of cognitive decline and depression in patients with CSVD, impairing indirectly overall functional capabilities of the patients, and making them more dependent. Timely and appropriate (according to current guidelines) treatment of metabolic syndrome may prevent or postpone its complications, including cognitive decline [14] [22] and depression [23]. Although this was not shown in the subset of patients with both CSVD and metabolic syndrome, it seems plausible that early treatment of metabolic syndrome in patients with CSVD would result with better functional outcome, and therefore decrease the burden of dependence on carers and society in general.

Our study has several limitations that may question the results and the conclusions drawn. First, the study was unicentric, which allow for introduction of bias driven by local practices; we tried to control it by strict following of national guidelines for hospital treatment of cerebrovascular diseases. Second, the study sample was small, and the study was not powered enough to reveal some subtle differences between the study groups, raising issue of possible false negative results. Our study was cross-sectional, with only one measurement of cognition and depression, what precluded capturing of their changes in time; therefore no causative relations and generalizable concusions should be drawn from the presented results until they recive confirmation from future cohort studies of sufficient size and duration.

In conclusion, our study showed that metabolic syndrome is associated with further worsening of already impaired cognition and existing depression in patients with the CSVD. Further studies should reveal whether intensive treatment of metabolic syndrome in patients with the CSVD may stop or even reverse cognitive impairment or progression of depression.

Conflict of interest statement: Authors state no conflict of interest

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