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THE SIGNIFICANCE OF INTERLEUKIN-6 AND TUMOR NECROSIS FACTOR-ALPHA LEVELS IN COGNITIVE IMPAIRMENT AMONG FIRST-EVER ACUTE ISCHAEMIC STROKE PATIENTS

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SUMMARY

Background: *Acute ischemic stroke (AIS) frequently results in the development of cognitive impairment, which quite often persists. The pathophysiological mechanisms involved in the development of cognitive impairment are only partially elucidated. The aim of this study was to evaluate the correlation between interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) serum levels with cognitive impairment in AIS patients.*

Subjects and methods: *This hospital-based case-control study was performed during December 2014 – May 2018. A total number of 130 randomly selected patients were prospectively recruited from the Department of Neurology, Clinical Center University of Sarajevo. The study examined 100 first-ever AIS patients, while 30 comprised the non-stroke control group of patients with discogenic lumbosacral radiculopathy. All participants were evaluated using the Mini-Mental State Examination, the Montreal Cognitive Assessment, the Frontal Assessment Battery, and the Addenbrooke's Cognitive Examination-Revised. Cognitive testing and laboratory analyses were performed within the first three days of admission in all patients while AIS patients were reassessed on the 15th day of hospitalization.*

Results: *Female stroke patients with cognitive impairment had significantly higher baseline levels of IL-6 ($p<0.017$), and TNF-α ($p<0.017$) than those without cognitive impairment. In the control measurement, a significant difference in IL-6 levels ($p=0.037$) in male and TNF-α levels ($p=0.042$) in female stroke patients with cognitive impairment was observed.*

Conclusions: *These findings indicate that p*ro-inflammatory cytokines *are probably implicated in the pathogenesis of cognitive decline in AIS patients.*

Key words: *cognitive impairment – cytokines – inflammation – ischemic stroke*

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INTRODUCTION

Acute ischemic stroke (AIS) is characterized by a sudden onset and rapid development of a focal neurologic signs. In addition to causing varying degrees of physical disability, ischemic stroke also impairs cognitive functions. It frequently results in the development of cognitive impairment, which quite often persists. More than two thirds of AIS patients and more than half of patients (57.7%) in the following 3 to 6 months after onset develop varying degrees of cognitive impairment (Saphira Nurani & Martini 2018, Dong et al. 2012, Li et al. 2020).

The pathophysiological mechanisms involved in the development of cognitive impairment are only partially elucidated. In particular, inflammation and oxidative stress, among others, are related to cognitive disorders and dementia. It has well been known that inflammation plays an important role in atherosclerosis since it causes endothelial dysfunction, plaque instability, and oxidetive stress. Oxidative stress and inflammation induced by risk factors for vascular cognitive impairment (VCI) are key pathogenetic elements in neurovascular dysfunction (Iadecola et al. 2009). Vascular oxidative stress causes endothelial dysfunction, which in turn increases vascular permeability, plasma protein extravasation, and cytokine production (He et al. 2020). In addition, vascular risk factors combined with oxidative stress and inflammation, influence blood-brain barrier permeability, thereby contributing to the development of VCI (Iadecola 2013).

Considering that cytokines have a major role in neuro-immuno-endocrine functions, it is assumed that these molecules affect cognition by various mechanisms. Cytokines have a neuroregulatory function and act as mediators for communication between the central nervous system and the immune system (Fard & Stough 2019). In this context, a question arises

whether measuring the levels of proinflammatory cytokines is indeed valuable in assessing the risk of development of cognitive impairment in AIS, whose pathogenesis remains yet to be fully clarified.

The aim of this prospective study was to evaluate the correlation between interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) serum levels with cognitive impairment in AIS patients.

SUBJECTS AND METHODS

Subjects

This prospective, case-control study was conducted at the Department of Neurology, Clinical Center University of Sarajevo (CCUS) between December 2014 and May 2018, and included a total of 130 patients. A randomly selected sample was consisted of 100 first-ever AIS patients and 30 non-stroke controls, suffering from discogenic lumbosacral radiculopathy.

Examined patients have to meet the following criteria: they were treated at the Department of Neurology CCUS in the observed period, older than 55 years of age, of both genders, with the signed voluntary consent to participate in the research.

The exclusion criteria were: 1) recurrent stroke; 2) hemorrhagic stroke; 3) age <55 years; 4) decreased level of consciousness; 5) previously diagnosed dementia or cognitive impairment; 6) history of depression and other psychiatric illness; 7) aphasia or severe dysphasia; 8) history of systemic diseases, 9) acute or chronic infection; 10) having severe visual or hearing impairment, and 11) having a malignant disease. There were additional exclusion criteria as follows: history of epilepsy, severe liver or renal failure, and significant acute medical condition at the time of consent. Patients who had previously a severe head injury, or who've had a previous brain surgery, patients with instable vital signs, or those who were unable to cooperate independently to complete the study were excluded. Also, patients with a body temperature above 37˚C during blood sampling, recent trauma or surgical intervention were excluded from the study due to the potential to affect the levels of inflammatory parameters.

Methods

The diagnosis of acute ischemic stroke was based on presenting symptoms and radiological findings (computed tomography – CT or magnetic resonance imaging - MRI of the brain).

Demographic data of participants including gender, age, education, and marital status were collected using questionnaire containing basic demographic questions. Additionally, some data were obtained by reviewing medical record for each patient. Presence of cerebrovascular risk factors and current medications were also collected, as well as neurological examinations and routine laboratory tests in the survey process, however these data were not included in the current study.

Both cognitive testing and laboratory analyses (IL-6 and TNF-α) were performed within the first 3 days of admission in all participants. Cognitive assessments were performed using the following scales: the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), the Frontal Assessment Battery (FAB), and the Addenbrooke's Cognitive Examination-Revised (ACE-R) (Folstein et al. 1975, Nasreddine et al. 2005, Dubois et al. 2000, Mioshi et al. 2006). The total score of the MMSE ≤23 indicates cognitive impairment, and a score of 24 and higher is classesed as normal. A MoCA score ≥26 points is considered normal, and a MoCA score ≤25 indicates cognitive impairment. A total FAB score <12 indicates impairment of executive functions, and the results are classified as low (<12) and normal FAB score (≥12). The recommended upper cut-off score of 88/100 for ACE-R was used for detecting cognitive decline, and the total ACE-R score is classified as low (<88) and normal ACE-R score (≥88) (Mioshi et al. 2006).

Based on baseline cognitive screening scores, AIS patients were divided into two groups: the first group with normal cognitive function (group I), and the second group with cognitive impairment (group II). The group III (n=30) was control and included patients with discogenic lumbosacral radiculopathy. In group I were 22 AIS patients, mean age 59.6±10.6 years, and 54.5% were men. Group II consisted of 78 AIS patients, at mean age of 69.5±9.5 years, 41 (52.6%) males and 37 (47.4%) females. A control group was composed of an equal number of males and females (15 or 50.0%).

Both the patients in group I and group II were reassessed including their cognitive functions and laboratory findings (IL-6, TNF-α) on the 15th day of hospitalization. The baseline cognitive assessments and laboratory analyses were performed only once in control group.

Biochemical tests

Peripheral venous blood samples from the cubital veins were collected for interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) determinations from all participants. Immediately after collection, samples were shipped to the central laboratory of the CCU for further analysis. After centrifugation, the serum was collected and stored at -20°C. Enzyme-linked immunosorbent assay (ELISA) was used to measure serum concentrations of IL-6 and TNF-α. The procedure was performed according to the manufacturer's instruction, and values were measured with a spectrophotometer (BioTec Elx-800).

Statistical Analysis

Statistical analyses were performed using the IBM Statistical Package for Social Sciences (SPSS) version 21.0 for Windows system (SPSS Inc. Chicago, Illinois, USA). Results are presented in tables and charts as absolute, relative and cumulative frequencies, arithmetic average (M) with standard deviation (SD), median (Me) and interquartile range (IQR, 25th to 75th percentiles).

Categorical variables were analyzed using Fisher's exact test and Pearson Chi-square test where appropriate. A Kruskal-Wallis test was conducted to determine if there were differences in values of tested parameters between three groups. The continuous variables were analyzed using Mann–Whitney U-test. One-factor covariance analysis (ANCOVA) was performed.

To examine the linear relationship between nominal and ordinal variables we used Pearson's correlation coefficient or Spearman rank correlation coefficient. The significance value for the omnibus tests was set to the conventional $p \leq 0.05$. Bonferroni correction was conducted for post-hoc analysis to reduce Type I error that can occur when performing multiple tests. $P<0.05$ was considered as statistically significant.

The protocol of this study was approved by the Ethics Committee of Clinical Center University of Sarajevo and was carried out in accordance with the ethical standards laid down in the Declaration of Helsinki. All participants were voluntarily admitted and gave an informed consent.

RESULTS

There was a statistically significant difference in age between the observed groups, $F(2,127)=28.096$, $p<0.001$. Post-hoc analysis (Bonferroni test) showed that patients in group II were statistically significantly older (M=69.5±9.5) compared to group I (M=59.6±10.6), ($p<0.001$), and controls (M=54.3±10.8), ($p<0.001$) (Figure 1). No significant differences in gender were found among the three groups ($\chi^2(2)=0.110$, $p>0.05$).

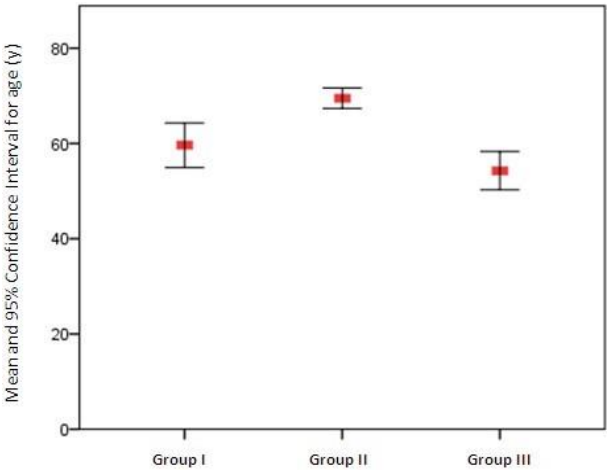

Figure 1. Age distribution of the three groups of subjects

Statistically significant difference was found in the serum levels of IL-6 in females ($\chi^2(2)=12.856$, $p=0.002$), but no differences were observed in males ($\chi^2(2)=3.272$, $p>0.05$). Female stroke patients with cognitive impairment had significantly higher baseline levels of IL-6 (Me=16.3; IQR=4.4 to 31.7) than females in group I (Me=1.2; IQR=0.0 to 8.7) (U=80, z=-2.739, $p<0.017$), and control group (Me=1.0; IQR=0.2 to 10.3) (U=134.5, z=-2.892, $p<0.017$) (Figure 2).

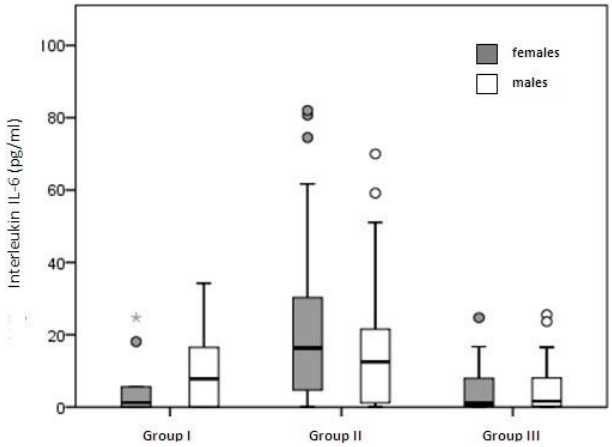

Figure 2. Values o*f IL-6 levels in serum by gender and group*

There was a significant difference in baseline TNF-α serum levels in women ($\chi^2(2)=9.710$, $p=0.008$), but not in men ($\chi^2(2)=0.885$, $p>0.05$). Serum TNF-α levels in female stroke patients were significantly higher with cognitive impairment (Me=6.7; IQR=0.1 to 13.0) than without cognitive impairment (Me=0.1; IQR=0.0 to 2.7) (U=76.5, z=-2.828, $p<0.017$) (Figure 3).

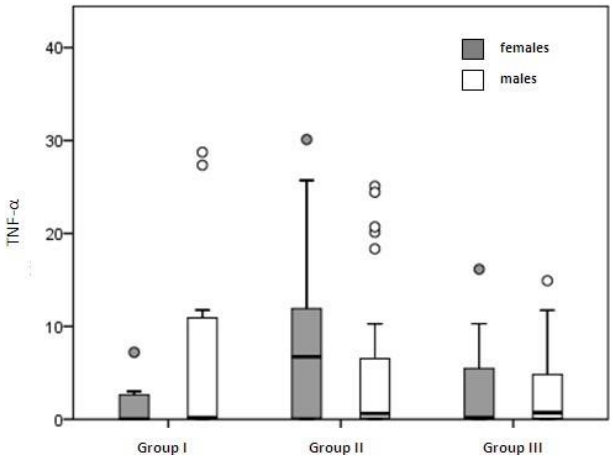

Figure 3. Values of TNF-α levels in serum by gender and group

Patients with cognitive impairment had statistically significantly higher values of IL-6 ($p=0.019$), and TNF-α ($p=0.021$) compared to the group without cognitive impairment on retesting without gender differences. After the mean levels for IL-6 and TNF-α have been

Table 1. Adjusted and unadjusted mean values and measures of dispersion of the laboratory tests (IL-6 and TNF-alpha) on the 15th day of hospitalization as a covariate by gender and patient group

On the 15th day in hospital	Group	Gender	Unadjusted values		Adjusted values		$F_{1,97}$	p	η^2_p
			M	S.E.	M	S.E.			
IL-6	group I	female	12.0	4.0	30.0	3.9	1.369	*0.248*	0.030
	group II		37.5	4.8	33.2	1.9			
	group I	male	16.1	4.9	22.0	3.5	4.606	*0.037*	0.084
	group II		32.3	4.4	31.0	2.9			
TNF-α	group I	female	4.4	1.3	11.1	2.5	4.234	*0.042*	0.074
	group II		17.1	2.3	15.3	1.3			
	group I	male	10.4	3.9	10.3	1.8	2.364	0.130	0.045
	group II		13.4	2.0	13.4	0.9			

adjusted for gender, stratification analysis demonstrated a statistically significant difference in IL-6 levels in men ($p=0.037$) and TNF-α levels in women ($p=0.042$). The adjusted levels of IL-6 were higher in male patients from group II (M=31.0) in comparison to males in group I (M=22.0). The adjusted levels of TNF-α were higher in female patients from group II (M=15.3) in comparison to females in group I (M=11.1) (Table 1).

A statistically significant positive correlation was found between IL-6 and TNF-α levels in patients with cognitive impairment (rho=0.665, $p<0.001$) (not shown). Furthermore, statistically significant negative correlations were observed between IL-6 level and cognitive tests scores: MMSE (rho=-0.511, $p<0.001$), MoCa (rho=-0.336, $p<0.01$), FAB (rho=-0.326, $p<0.01$), and ACE-R (rho=-0.387, $p<0.001$), as well as between TNF-α level and all cognitive tests scores: MMSE (rho=-0.520, $p<0.001$), MoCa (rho=-0.390, $p<0.001$), FAB (rho=-0.389, $p<0.001$), and ACE-R (rho=-0.358, $p<0.01$) (not shown).

DISCUSSION

In present study, the association between serum proinflammatory cytokine levels and development of cognitive decline in AIS patients was analyzed. The results showed that female patients with cognitive impairment had significantly higher baseline serum concentrations of IL-6 ($p<0.017$) compared to women in the other two groups. Furthermore, female patients with cognitive impairment showed significant higher TNF-α level at baseline ($p<0.017$) in comparation to females from group I. Statistical significance was found in the values of IL-6 in men ($p=0.037$), and TNF-α in women ($p=0.042$) with cognitive impairment at the second measurement of cytokine levels.

The PROSPER study demonstrated that higher circulating levels of IL-6 were associated with cognitive impairment in old age (Mooijaart et al. 2013). Such results are comparable with the results of this study, even though the study was conducted using different samples. Economos et al. (2013) also studied this problem in their multiethnic cohort study, obtaining similar findings regarding the relationship between increased levels of IL-6 and cognitive impairment among older participants. Zhao et al. (2012) emphasize the importance of IL-6 levels in the early diagnosis of amnestic mild cognitive impairment (aMCI), as well as its negative correlation with decline in cognitive performance.

Spalleta et al. (2013) examined the relationship between levels of circulating IL-6 and the severity of neuropsychiatric symptoms in AIS patients and found that IL-6 plays an important role in the development of depressive symptoms, apathy/amotivation, somatic symptoms of depression, as well as significant role in neurological/functional impairment, which further results in a worse patient outcome.

Finally, in recent researches, Kulesh et al. (2016, 2018) analyzed the relationship between the markers of neuroinflammation and neurodegeneration with cognitive impairment in AIS patients. All patients, regardless of their cognitive status, had increased serum IL-10 levels in comparison with the control group, whereas the patients with executive dysfunction had higher serum IL-6 levels, and levels of IL-1β and IL-10 in the cerebrospinal fluid (CSF) compared to the patients with normal cognition. The results of the current study are in line with the above-referenced results in regards to the serum IL-6 levels, while concentrations of other proinflammatory cytokines in serum as well as CSF cytokines levels have not been assessed.

In this study, the female AIS patients with cognitive impairment had a statistically higher serum level of TNF-α in both their first and second laboratory measurements. These findings confirm results from previous studies by Trollor et al. (2010) and Zuliani et al. (2007), which also found increased levels of TNF-α in patients with mild cognitive impairment and vascular dementia. Their results are consistent with the findings of this study, even though the sampled groups were different.

The researchers so far have demonstrated the gender differences in certain cognitive abilities related to hormonal influences. Women presumably have a higher risk of developing cognitive impairment due to the changes in levels of ovarian hormones. More precisely, low levels of estradiol are linked to impairment in global cognitive functions and verbal memory. Estradiol is believed to have a neuroprotective function and can limit the damage caused by oxidative stress (Myers 2008).

A statistically significant negative correlation was noted between the serum levels of IL-6, on one hand, and the scores of all screening cognitive tests (i.e. the severity of cognitive impairment) on the other hand, in the group of patients with cognitive impairment. Alley et al. (2008) report a negative correlation between cognition and inflammation, i.e. the relationship between serum IL-6 and CRP levels with the scores of cognitive tests in the older population, which is in accordance with the results of this study. Despite the different sample groups, the study by Athilingam et al. (2013) including patients with chronic heart failure demonstrated a negative correlation between IL-6 and CRP serum levels with scores on the MoCA, confirming our findings. The multiethnic cohort study showed a negative correlation between the serum levels of IL-6 and MMSE score (Wright et al. 2006), with the results identical to those obtained in present study. The findings of this research are consistent with previous studies (Alley et al. 2008, Athilingam et al. 2013, Wright et al. 2006), despite the fact that different sample groups were examined.

Spearman's correlation showed a statistically significant negative correlation between serum TNF-α values and total scores of all cognitive tests in patients with cognitive impairment. These results support the hypothesis that the increased serum levels of proinflammatory cytokines are associated with cognitive decline.

In the initial assessment, cognitive impairment was related to higher levels of assessed proinflammatory cytokines in females. Furthermore, the second, final assessment showed statistically higher levels of IL-6 in males, while the relationship between the serum levels of TNF-α and females remained unchanged. Obtained results indicate a significant correlation between serum IL-6 and TNF-α levels and cognitive impairment in AIS patients, but also alterations of cytokine levels linked to the gender differences. Based on these observations we can confirm that cognitive impairment correlates with the evaluated biomarkers, with the emphasis on the different dynamic of the markers in males and females, which further implies the probable complex interaction between the immune and endocrine systems.

According to available literature, this study is the first to examine the relationship between proinflammatory cytokines (IL-6 and TNF-α) and cognitive impairment in AIS. The advantages of the study include a homogeneous sample, i.e. only patients with the first-ever AIS were included, without previous medical conditions which might influence the production of cytokines or stimulate inflammatory processes. Moreover, the fluctuations of the assessed inflammatory parameters which do not correlate with cognitive changes were excluded by reassessing the cognitive functions and laboratory findings.

It would be advisable to retest cognitive function in these patients after a certain time frame to obtain insight in development of cognitive disorder, with the intent to aid early detection of vascular dementia. Timely diagnosis, follow-up and treatment of vascular cognitive impairment in AIS patients should be instituted as an everyday clinical practice, leading to a better clinical outcome.

CONCLUSIONS

The results of this study showed that AIS patients with cognitive impairment has statistically higher serum IL-6 and TNF-α levels compared with patients without cognitive impairment. These findings indicate that proinflammatory cytokines are probaby implicated in the pathogenesis of cognitive decline in AIS patients.

The use of cognitive assessment tools, as well as determining the serum concentrations of pro-inflammatory cytokines IL-6 and TNF-α allow timely detection of cognitive decline which can further contribute in predicting the potential progression from early symptoms of cognitive impairment to vascular dementia.

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Conflict of interest: None to declare.

Contribution of individual authors:

Nataša Loga-Andrijić: obtaining permissions from the Ethics Committee, design of the study, sample collection, statistical analyses, literature searches and analyses, manuscript writing.

Novica T. Petrović: design of the study, statistical analyses, interpretation of data.

Snežana Filipović–Danić: literature searches and analyses, interpretation of data.

Snežana Marjanović & Vekoslav Mitrović: statistical analyses, interpretation of data.

Svjetlana Loga-Zec: sample collection, literature searches and analyses, manuscript writing.

All authors approval of the final version.

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