ijlpr 2022; doi 10.22376/ijpbs/lpr.2022.12.6.SP23.L51-56

International Journal of Life science and Pharma Research

ISSN 2250-0480

Research Article

The Role Of Fibrosis And Immune Inflammation In Depression In Patients With Ischemic Stroke

Olga A. Osipova [1*], Elena V. Gosteva [1,2], Nikolai I. Kluishnikov[1,3], Elena V. Kaliuzhnaya[1] and Alexey A. Shabalin[4]

[1]"Belgorod State National Research University", Belgorod, Russia, 308015, 85, Pobeda str., Belgorod

[2] "Voronezh State Medical University named after N.N.Burdenko "394036 10, Studencheskaya, str., Voronezh

[3] Voronezh City Clinical Hospital of Emergency Medical Care ? 8, 394090, 90 Rostovskaya str., Voronezh.

[4] Kursk State Medical University 305 041, 3, K. Marxs, str., Kursk.

Abstract: Nowadays, Stroke is regarded as the second major cause of death and the third major cause of morbidity globally. The ischemic stroke (IS) is among the most fatal kind of strokes. Thus, due to the importance of this subject, this article aims to analyze the role of fibrosis markers (matrix metalloproteinase-9, tissue inhibitor of matrix metalloproteinases-1), cytokines (tumor necrosis factor-α, interferon-γ, monocytic chemoattractant protein-1) in the development of post-stroke depression in elderly patients with arterial hypertension (AH). To that end, the study included 114 elderly patients with the first acute ischemic stroke; the average age of the patients was 68 ± 7 years. The control group consisted of 20 older people without hypertension and a history of stroke. The level of matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) was determined by ELISA (ELISA Kit, USA); the level of tumor necrosis factor-α (TNF-α), interferon-γ (INF-γ), monocytic chemoattractant protein-1 (MCP-1) - JSC "Vector-Best", Russia. After 3 months of observation of patients, post-stroke depression (PD) developed in 50 people. (43.8%). Patients who developed PD were significantly older (9.4%, p <0.05), a higher body mass index by 12.2% (p <0.05), a glycemic level by 16.1% (p <0, 05), triglycerides by 14.0% (p <0.05), LDL by 12.8% (p <0.05) than in patients without depression. Patients with ischemic stroke and PD had higher levels of cytokines - TNF-α by 23.8% (p <0.01), INF-γ by 17.5% (p <0.01), MCP-1 by 17, 6% (p <0.01), the level of MMP-9 was higher by 15.3% (p <0.05), TIMP-1 - by 11.4% (p <0.05). Thus, in elderly patients with hypertension with ischemic stroke, the level of fibrosis and inflammation markers may have a prognostic value in developing post-stroke depression. Hence, this article could greatly contribute to the alleviation of depression in patients with ischemic stroke.

Keywords: Post-Stroke Depression, Fibrosis Markers And Cytokines.

***Corresponding Author**

Olga A. Osipova , Belgorod State National Research University", Belgorod, Russia, 308015, 85, Pobeda str., Belgorod

Received On 04 August 2022

Revised On 09 September 2022

Accepted On 16 September 2022

Published On 20 September 2022

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Olga A. Osipova, Elena V. Gosteva , Nikolai I. Kluishnikov, Elena V. Kaliuzhnaya and Alexey A. Shabalin , The Role Of Fibrosis And Immune Inflammation In Depression In Patients With Ischemic Stroke.(2022).Int. J. Life Sci. Pharma Res.12(6.SP23), L51-56 http://dx.doi.org/10.22376/ijpbs/lpr.2022.12.6.SP23.L51-56

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1. INTRODUCTION

Stroke is the second leading cause of death and the third leading cause of morbidity worldwide [1]. Among all strokes, ischemic stroke (IS) comes for approximately 80% to 85%. After a stroke, patients face both physical and neuropsychiatric problems. Sudden functional deficits, fear of emotional instability and death, and the need for rehabilitation can lead to stress and depression. Post-stroke depression (PD) is an emotional disorder that often occurs in patients during the first three months after a stroke [2, 3]. Depression negatively affects the patient's ability to participate in rehabilitation therapy and is closely associated with further impairment of physical and cognitive recovery [4]. The pathogenesis of post-stroke depression is extremely complex and can result from the interaction of many factors. Activation of the immune system during a stroke triggers a cytokine production cascade [5] that increases excitotoxic neuronal death as a result of over-activation of the glutamatergic system. Subsequently, the interaction between cytokines, glucocorticoids, and neurotrophils leads to a decrease in hippocampal neurogenesis, which has been proven to be important for mood control [6]. A recent meta-analysis established the presence of neuroinflammation in depressed patients due to increased levels of proinflammatory cytokines in the brain parenchyma [7]. An active search continues for the neurobiological mechanisms of depression, with some studies providing evidence for the role of inflammatory responses in the etiology of depression [8, 9]. Analysis of literature data from October 1977 to December 2017 showed the participation of potential markers of inflammation in the diagnosis of PD [10]. According to the data obtained, up to 12 months after a stroke, elevated markers of inflammation, such as highly sensitive C-reactive protein, ferritin, neopterin and glutamate, as well as pro-inflammatory cytokines studied in blood serum (TNF-α, IL-1β, IL-6, IL -18, INF-γ) in patients with PD. Studies have shown that in the acute phase of ischemic stroke, pro-inflammatory mediators (in particular TNF-α), promote the expression of MMP-9 and enhance its activity. Activated MMP-9 destroys the extracellular matrix, promotes the breakdown of the blood-brain barrier, which enhances the inflammatory response [11]. Tissue inhibitor of metalloproteinase-1 is an endogenous inhibitor of MMP-9 and is involved in the processes of degradation of the extracellular matrix, inflammation, fibrosis, and apoptosis in patients with cardiovascular diseases [12]. The expression of TIMP-1 is significantly increased after acute cerebral ischemia and is involved in neurodegeneration [13]. New data indicate that both TIMP-1 and MMP-9 are promising cardiovascular biomarkers, whose circulating levels significantly increase after acute cerebral ischemia and play an important role in predicting the development of post-stroke depression in patients with ischemic stroke [14]. However, changes in the level of markers of inflammation and fibrosis in the blood serum in patients with acute IS and their relationship with the development of post-stroke depression remain not fully developed. Thus, markers of fibrosis, cytokines are significantly involved in the pathogenesis of ischemic stroke, and serum levels may be possible biomarkers for predicting the risk of post-stroke depression in elderly patients. Overall, based on what was mentioned earlier, this study mainly revolves around analyzing the role of fibrosis markers (MMP-9, TIMP-1), cytokines (TNF-α, INF-γ, MCP-1) in the development of depression in patients with ischemic stroke in old age. The article seeks to ascertain whether an increased level of markers of inflammation and fibrosis can raise the detection rate of stroke patients.

2. MATERIALS AND METHODS

The study was carried out on the basis of the laboratory "Problems of Aging" of the National Research University BelSU, the Belgorod Regional Hospital of St. Joasaph, and the neurological department of the emergency hospital No. 8 in Voronezh. A prospective, cohort study was carried out, which included 114 patients. The inclusion criteria for the study were elderly patients with arterial hypertension who were admitted to the hospital in the acute period of the first cerebral stroke. Exclusion criteria: severe physical illness, refusal to participate in the study. Within three months, 2 patients dropped out of the study due to refusal to follow-up. Thus, an assessment of the studied indicators was carried out in 112 people (98.2%). The average age of the patients is 68 ± 7 years. The severity of the patients' condition was assessed using the NIHSS scale[7-9], the mean score was 5 ± 3, which corresponded to mild severity. The observation period was 3 months. The control group consisted of 20 elderly people without hypertension and a case history of stroke. The level of MMP-9 and TIMP-1 was determined by ELISA (ELISA Kit, USA); level of TNF-α, INF-γ, MCP-1 - JSC "Vector-Best", Russia[2,9,12]. The patients were examined on the 2nd day (± 1 day) of stroke and 3 months after the stroke. Depressive disorders were diagnosed based on self-assessment on the Tsung -SDS and DSM-V criteria[11-15]. All patients received identical basic therapy aimed at correcting central and cerebral hemodynamics, normalizing homeostasis, and improving perfusion of brain tissue.

3. STATISTICAL ANALYSIS

Statistical analysis was performed using the STATISTICA 10.0 package. Quantitative indicators are presented as median (Me), interquartile ranges (Q25%; Q75%), continuous quantitative values were expressed as mean ± SD, differences were considered significant at $p < 0.05$.

Plus, the ethics committee of Belgorod State National Research University has proved this study and claimed that there are no ethical issues.

4. RESULTS

Table 1 shows the results of a study of markers of fibrosis and inflammation in the serum of patients with ischemic stroke.

Table 1. The content of fibrosis markers and pro-inflammatory cytokines in blood serum in patients with ischemic stroke (Me [Q25%; Q75%])

Indicators, units measurements	Control group (n=20)	IS patients (n=112)
TNF-α, pg / ml	8.7 (6.8; 11.3)	34.9 (28.0; 42.4) ***

INF-γ, pg / ml	18.6 (14.4; 24.7)	76.8 (56.9; 95.4) ***
MCP-1, pg / ml	79.5 (55.3; 104.6)	216.1 (176.5; 249.8) ***
MMP-9, ng / ml	108 (84; 132)	267 (224; 301) ***
TIMP-1, ng / ml	216 (178; 256)	397 (345; 430) ***
MMP-9 / TIMP-1	0.50 (0.45; 0.53)	0.67 (0.63; 0.69) **

Note: ** p <0.01, *** p <0.001 - compared with the control group

The level of cytokines in the blood serum of patients with IS in the elderly is significantly higher: TNF-α by 4.0 times (p <0.001), INF-γ by 4.1 times (p <0.001), MCP-1 by 2.7 times (p <0.001) compared with the control group. The initial level of MMP-9 is 2.5 times higher (p <0.001), TIMP-1 is 1.8 times (p <0.001), the ratio of MMP-9 / TIMP-1 is 1.3 (p <0.01) times higher than in the control group. After 3 months, we assessed post-stroke depression. So, in elderly patients, early post-stroke depression developed in 50 people. (43.8%).

Table 2 presents the clinical and laboratory characteristics of the studied groups of patients with ischemic stroke, depending on the development of post-stroke depression.

Table 2. Clinical and laboratory characteristics of patients with ischemic stroke included in the study, depending on the development of post-stroke depression

Indicators, units of measurement	IS without PD, (n = 62, people)	IS with PD (n = 50, people)
Male / female, pers	36/26	28/22
Age, years	64 (61; 67)	70 (65; 74)
Ischemic heart disease, pers. (%)	14 (22.6%)	24 (48%)
DM 2, pers. (%)	6 (9.7%)	10 (20%)
BMI, kg / m2	28.7 (25.0-29.1)	32.2 (28.3-35.1)
Hypertriglyceridemia, pers.	30 (48.4%)	38 (76%)
NIHSS	4 (3; 6)	6 (5; 7)

Note: IS - ischemic stroke, DM - diabetes mellitus, BMI - body mass index, TG - triglycerides

Patients with ischemic stroke who developed post-stroke depression were significantly older by 9.4% (p <0.05), more often had diabetes mellitus by 10.3% (p <0.05), hypertriglyceridemia by 27.6% (p <0.01), had a 50% higher NIHSS score (p <0.01) than patients without PD. In patients with PD, the level of glycemia is higher by 16.1% (p <0.05), triglycerides by 18.0% (p <0.05), LDL by 12.8% (p <0.05) than the group patients without depression (Figure 1).

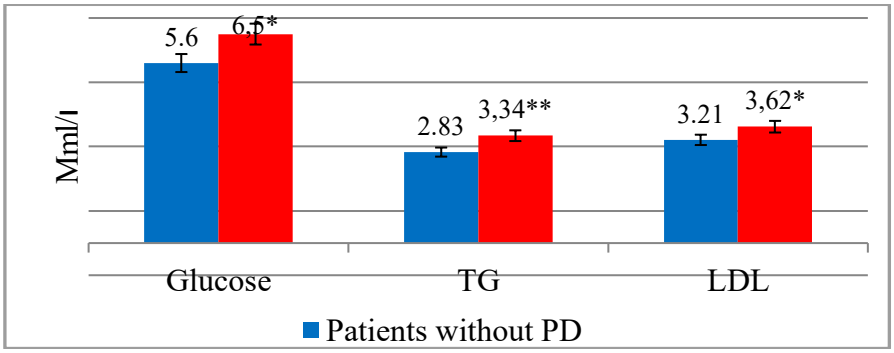

Fig 1 - the level of glucose, triglycerides and low density lipoproteins, depending on the presence of PD; * p <0.05, ** p <0.01 - compared with patients without PD

In a comparative analysis of markers of fibrosis and inflammation in elderly patients with developed post-stroke depression, it was found (Table 3) that the level of TNF-α in the blood serum was 23.8% (p <0.01), INF-γ by 17.5%. (p <0.01), MCP-1 by 17.6% (p <0.01), MMP-9 by 15.3% (p <0.05), TIMP-1 by 11.4% (p <0.05) is higher than in patients without PD.

Table 3. The content of fibrosis markers and pro-inflammatory cytokines in the blood serum of patients depending on the development of post-stroke depression (Me [Q25%; Q75%])

Indicators, units of measurement	IS patients without PD (n=62)	IS patients with PD (n=50)
TNF-α, pg / ml	31.1 (28.0; 42.3)	38.5 (35.1; 42.4) **
INF-γ, pg / ml	69.7 (56.9; 80.3)	81.9 (71.2; 95.4) **
MCP-1, pg / ml	202.8 (176.5;229.3)	238.4 (226.5;249.8) **
MMP-9, ng / ml	242 (224; 264)	279 (259; 301) *
TIMP-1, ng / ml	367 (345; 385)	409 (385; 430) *

MMP-9 / TIMP-1	0.65 (0.63; 0.69)	0.68 (0.65; 0.70)

Note: * p <0.05, ** p <0.01 - compared with patients without PD

There were no significant differences in the MMP-9 / TIMP-1 ratio between the study groups of patients. After 3 months of observation (Figure 2), it was found that in elderly patients with post-stroke depression, the serum level of MCP-1 remained 1.45 times, TNF-α 1.52 times, INF-γ 1.49 times higher than in groups of patients without PD.

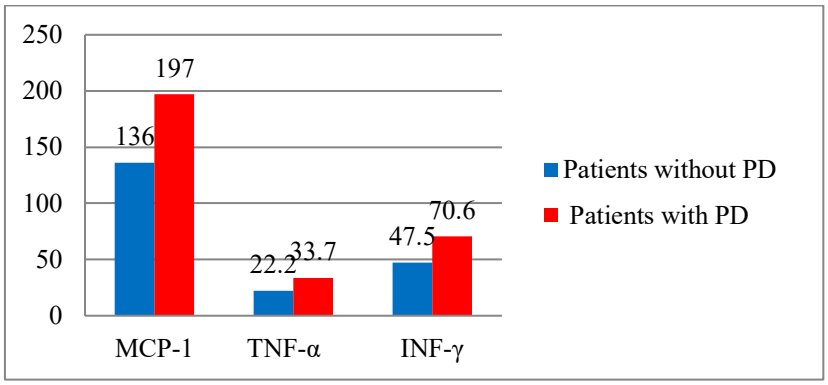

Fig 2. The level of MCP-1, TNF-α, INF-γ in blood serum after 3 months, depending on the presence of PD; *** p <0.001 compared with patients without PD

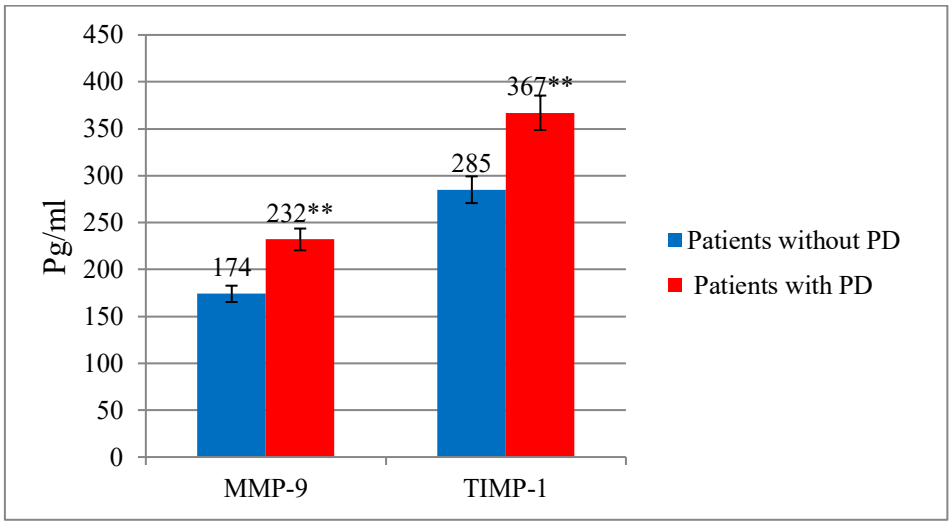

Fig 3. The level of MMP-9, TIMP-1 in the blood serum after 3 months, depending on the presence of PD; ** p <0.01 compared with patients without PD

When examining patients with post-stroke depression in the elderly after 3 months of observation, it was found that the level of MMP-9 remained 1.33 times, TIMP-1 1.3 times higher than the group of patients without PD (Figure 3)

5. RESULTS AND DISCUSSION

A growing body of evidence points to the important role of pathophysiological changes following ischemic brain injury. The resulting inflammation enhances the synthesis of cytokines determined both in the damaged brain tissue and in the peripheral blood [5], which cause additional damage to the brain cells [3]. This study confirms the data that the level of cytokines increases in patients with ischemic stroke. The results obtained are of interest depending on the development of early PD in elderly patients.

TNF-α, on the one hand, is an important mediator of inflammation after cerebral ischemia; on the other hand, it plays a key role in the pathophysiological mechanisms leading to the development of stroke [15, 16]. The progression of atherosclerosis (as the main factor in the development of stroke) always directly correlates both with the level of TNF-α in the blood and with a local increase in the production of TNF-α in the atherosclerotic plaque [17]. Our study revealed a significant increase in the serum TNF-α level in patients with ischemic stroke with early post-stroke depression by 23.8% (p <0.01) compared with patients without PD[5-7]. After 3 months, in patients with PD, the level of TNF-α decreased by 12.5% and in patients with PD and by 28.6% without PD. Analysis of the data obtained showed an increase in the level of MCP-1 in the blood serum of patients with IS. We found that patients who subsequently developed PD had higher serum MCP-1 values by 17.6% (p <0.01) than without PD. After 3 months, in patients with PD, the level of MCP-1 decreased by 17.4% and by 32.9% without PD. More and more data indicate a high expression of INF-γ in the process of atherogenesis, and the participation of this cytokine in the

pathogenesis of ischemic stroke [18-20]. The study revealed a more pronounced increase in the content of INF-γ in the blood serum of IS patients with PD by 17.5% compared with patients without PD. After 3 months, in patients with PD, the level of INF-γ decreased by 13.8% in old age in IS patients with PD and by 31.9% in patients with IS without PD. Our results are fully consistent with the literature data, which demonstrated an increased release of proinflammatory cytokines. In experimental models of cerebral ischemia, as well as in patients with acute stroke, increased production of cytokines correlated with a larger ischemic area and worse neurological outcome [16, 19]. In cerebral ischemia, the occurrence of pathological profibrotic effects is interrelated with an increased release of proinflammatory cytokines and activation of immune cells [20]. With a stroke, an ischemic cascade is triggered in the damaged tissue, as a result of the interaction between immune cells, glial cells and matrix components, an increase in the permeability of the blood-brain barrier occurs, which contributes to a persistent inflammatory process due to the release of inflammatory mediators such as INF-γ, TNF-α, which in turn, enhances neuronal damage [21, 22]. MMP-9 has been shown to be involved in the complex pathophysiology of ischemic stroke, including maturation, degradation, and rupture of atherosclerotic plaques [23]. The expression of TIMP-1 is significantly increased after acute cerebral ischemia and is involved in neurodegeneration [13]. Analysis of the data obtained in our study showed an increase in the level of MMP-9 in the blood serum of patients with IS. We found that patients who subsequently developed PD had higher serum MMP-9 values by 15.3% ($p < 0.01$) than without PD. After 3 months, in patients with PD, the level of MMP-9 decreased by 16.8% and by 17.9% without PD. In a study by Ramos-Fernandez M. et al (2011) also observed significant differences in the level of MMP-9 between patients with IS and healthy controls; the level of MMP-9 was significantly increased after the onset of stroke, and this level correlated with the volume of myocardial infarction, the severity of stroke, and functional outcome. That is, MMP-9 is a possible marker of ongoing cerebral ischemia [24]. It was proved that the level of TIMP-1 in patients with IS was 11.4%. After 3 months, in patients with PD, the TIMP-1 level decreased by 10.3% and by 22.3% without PD.

6. CONCLUSION

Over the course of this study, it was attempted to investigate the role of fibrosis markers (matrix metalloproteinase-9, tissue inhibitor of matrix metalloproteinases-1), cytokines (tumor necrosis factor-α, interferon-γ, monocytic chemoattractant protein-1) in the development of post-stroke depression in elderly patients with arterial hypertension (AH). To accomplish that aim, a prospective, cohort study was carried out, which included 114 patients. The results obtained reveal that adding the determination of the level of cytokines (TNF-α, INF-γ, MCP-1) and fibrosis markers (MMP-9, TIMP-1) in serum to laboratory studies can significantly improve the prediction of the risk of PD development. Moreover, the results demonstrate that an increased level of markers of inflammation (TNF-α, INF-γ, MCP-1) and fibrosis (MMP-9, TIMP-1) can increase the detection rate of stroke patients who need special attention to detect the development of PD. So, this article could be of great help to the treatment of post-stroke depression in elderly patients. For the future studies, It seems vital to explore the pathogenesis and related influencing factors, establish appropriate diagnostic criteria and scales, and determine the best preventive and therapeutic measures.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

8. AUTHORS CONTRIBUTION

O.A.O. and E.V.G. designed the study. O.A.O., E.V.G., N.I.K., E.V.K. and A.A.S. performed the experiments. E.V.K. and A.A.S. were involved in planning and supervised the work. O.A.O., E.V.G., N.I.K., E.V.K. and A.A.S. contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript

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