The role of markers of fibrosis and immune inflammation in the development of post-stroke depression in elderly patients with chronic kidney disease and acute ischemic stroke

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Abstract. Stroke continues to be the most important medical and social problem due to its high share in the structure of morbidity and mortality. Neuroinflammation is characterized by increased levels of proinflammatory cytokines in the brain parenchyma. An increase in the level of MMP-9 in peripheral blood correlates with the severity of depression. **Purpose of the study** – to determine the features of the concentration of fibrosis markers (MMP-9) and immune inflammation (TNF-α, IL-1β, INF-γ) in the blood serum of elderly patients with chronic kidney disease and ischemic stroke, depending on the development of post-stroke depression. **Material and research methods.** The study included 98 people, of whom 78 patients with chronic kidney disease (CKD, C2, A2) with acute ischemic stroke (IS) and 20 people in the control group, comparable in age without chronic kidney disease and ischemic stroke in history. The average age of the patients was 68 ± 6 years. Post-stroke depression during follow-up developed in 34 people. (43.6%), 44 people (56.4%) did not show signs of PSD. The average NIHSS score was 8 ± 5, which corresponded to mild (20 people, 25.6%) and moderate (58 people, 74.4%) severity. The concentration of MMP-9 in serum was determined by ELISA using the Human MMP-9 kit (ELISA Kit, USA), the level of IL-1β, TNF-α, INF-γ - using a set of reagents for ELISA CJSC "Vector-Best", Russia. **Results**. The level of IL-1β in the blood serum of patients with CKD, IS with PSD was 1.3 times ($p < 0.001$) higher, TNF-α was 1.6 times higher ($p < 0.001$), INF-γ was 1.3 times higher than in the group of patients with CKD, IS without PSD ($p < 0.001$). The level of MMP-9 in CKD, IS patients with PSD is 1.4 times higher than in the group of CKD, IS patients without PSD ($p < 0.01$). **Conclusion.** Thus, the addition of the determination of the serum level of markers of fibrosis (MMP-9) and immune inflammation (IL-1β, TNF-α, INF-γ) can improve the prediction of the risk of post-stroke depression in elderly patients with chronic kidney disease

and ischemic stroke. In addition, the results obtained can help in identifying elderly patients with CKD with IS, who need special attention for the early detection of post-stroke depression.
Keywords: ischemic stroke, kidney disease, depression

Stroke continues to be the most important medical and social problem due to its high share in the structure of morbidity and mortality [1]. Patients with chronic kidney disease have multiple risk factors that provoke vascular endothelial damage, oxidative stress, inflammation, fibrosis of the extracellular matrix, which leads to the progression of atherosclerosis, arterial hypertension, and aggravation of neurodegeneration. Chronic kidney disease, influencing the pathogenetic mechanisms of stroke development, worsens the results of recovery, causing cognitive impairment, anxiety, and depression. In addition, sudden onset of functional deficits, emotional instability, fear of death, and the need for rehabilitation can lead to stress and depression. Post-stroke depression (PSD) is the most common emotional disorder after stroke, affecting about 1/3 of patients, and has an important impact on the course, recovery and prognosis of stroke [2, 3]. Depression symptoms are most common in the first 3–6 months after a stroke, which leads to a decrease in the effectiveness of rehabilitation therapy, difficulties in physical and cognitive recovery, especially in older age groups [4, 5]. Enache D et al (2019) showed that patients with depression have neuroinflammation, which is characterized by an increased level of proinflammatory cytokines in the brain parenchyma [6]. In addition, studies by Beroun A (2019) showed an increase in the level of matrix metalloproteinase-9 (MMP-9) in the peripheral blood in patients with depression, and their correlation with the severity of depression [7]. Thus, MMP-9, interleukins are significantly involved in the pathogenesis of post-stroke depression (PSD - PSD) and may be possible biomarkers for predicting the risk of PSD development.

Purpose of the study – to determine the features of the concentration of fibrosis markers (MMP-9) and immune inflammation (TNF-α, IL-1β, INF-γ) in the blood serum of elderly patients with chronic kidney disease and ischemic stroke, depending on the development of post-stroke depression.

Material and research methods

The study was carried out on the basis of the neurological department of the emergency hospital № 8 in Voronezh. The study included 98 people, of whom 78 patients with chronic kidney disease (CKD, C2, A2) with acute ischemic stroke (IS) and 20 people in the control group, comparable in age without chronic kidney disease and ischemic stroke in history. The inclusion criteria for the study were elderly patients with chronic kidney disease (C2, A2) who were admitted to the hospital in the acute period of the first cerebral stroke. Exclusion criteria -

refusal to participate in the study. The average age of the patients was 68±6 years. Post-stroke depression during follow-up developed in 34 people. (43.6%), 44 people (56.4%) did not show signs of PSD. The diagnosis of stroke was established on the basis of anamnesis, clinical criteria (severity of cerebral and focal symptoms); additional laboratory and instrumental research methods. The severity of the patients' condition was assessed using the NIHSS scale, the mean score was 8±5, which corresponded to mild (20 people, 25.6%) and moderate (58 people, 74.4%) severity. Upon admission, the concentration of MMP-9 was determined by ELISA using highly sensitive Human MMP-9 kits (ELISA Kit, USA). Determination of the level of IL-1β, TNF-α, INF-γ was carried out using a set of reagents for ELISA CJSC "Vector-Best", Russia. Registration of neurological and mental status was carried out on days 1-3 and 90 days (±2 days) after the stroke. Depressive disorders were diagnosed based on the DSM-V criteria [8]. All patients received identical complex therapy aimed at correcting central and cerebral hemodynamics, normalizing homeostasis, and improving perfusion of brain tissue.

Statistical processing was carried out using the "Microsoft Excel 2016" software package. Quantitative indicators are presented as median (Me), interquartile ranges (Q25%; Q75%), continuous quantitative values were expressed as mean ± SD. Comparison of quantitative variables with a normal distribution of the trait was carried out using the Student's t-test, the differences were considered significant at a significance level of $p < 0.05$.

Results and its discussion

Within three months, 5 people (6.4%) dropped out of the study, 3 of them due to refusal to follow-up, 2 people with a recurrent stroke. Thus, an assessment of the studied indicators was carried out in 73 people. (93.6%).

Table 1 presents the clinical and laboratory characteristics of the studied groups of CKD patients with ischemic stroke, depending on the development of post-stroke depression.

Table 1 Clinical and laboratory characteristics of patients with chronic kidney disease with ischemic stroke included in the study, depending on the development of post-stroke depression.

Indicators, units of measurement	IS without PSD, (n=40,people)	IS with PSD (n=34, people)
Men/women, people	28/12	24/10
AH, people. (%)	30 (75%)	32 (94.1%)*
IHD, people. (%)	10 (25%)	10 (29.4%)
DM 2 types, people. (%)	5 (12.5%)	6 (17.6%)
AO, people. (%)	12 (30%)	12 (35.3%)

Age, years	64 (61; 67)	70 (65; 74)*
BMI, kg/m^2	29.7 (27.0-32.1)	30.2 (27.3-33.8)
Glucose, mmol/l	5.4 (4.7-7.2)	5.9 (5.2-7.4)*
TG, mmol/l	1.96 (1.54-2.37)	2.84 (2.09-3.37)**
LDLP, mmol/l	2.80 (2.45-3.17)	3.47 (2.88-3.87)**
NIHSS	5 (3; 7)	7 (3; 9)**

Note: AH – arterial hypertension; AO- abdominal obesity, IHD – ischemic heart disease; IS – ischemic stroke, BMI – body mass index, LDLP – low density lipoproteins, PSD – post-stroke depression, DM – diabetes mellitus, TG – triglycerides; * p<0,05; **p<0,01 – between the studied groups of patients

Elderly patients with CKD and ischemic stroke who developed post-stroke depression were significantly older (Δ8.6%, p <0.05) than without PSD, more often had arterial hypertension (Δ20.3%, p <0.01), hyperglycemia (Δ9.3%, p <0.05), hypertriglyceridemia (Δ31.0%, p <0.01), higher LDLP values (Δ19.3%, p <0.05), higher score for NIHSS (Δ28.6%, p <0.01).

Recently, the occurrence of neuroplastic changes in the brain is associated with an increased production of pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF-α), which inhibit the indolamine-2,3-dioxygenase involved in the synthesis of serotonin, which helps to inhibit the synthesis neurotransmitters. In this regard, we have studied the content of IL-1β, TNF-α and INF-γ in blood serum. When analyzing the results obtained, it was revealed that in elderly patients with CKD and ischemic stroke, the indicators of inflation were significantly higher than in the control group. Thus, the level of IL-1β in the blood serum in the control group (CG) was 20.9 (14.9; 27.1) pg/ml, in patients with CKD, IS without PSD 55.1 (47.9; 65, 2) pg/ml, which is 2.6 times higher than in CG (p <0.001), in patients with CKD, IS with PSD 71.2 (58.3; 83.3) pg/ml, which is higher than CG in 3.4 times (p <0.001), and 1.3 times than in the group of patients with CKD, IS without PSD (p<0.001).The serum TNF-α content in the control group was 5.2 (3.4; 6.8) pg/ml, in patients with CKD, IS without PSD 12.1 (9.9; 14.8) pg/ml, which is 2.3 times higher than the CG (p <0.001), in patients with CKD, IS with a PSD of 19.5 (13.0; 24.2) pg/ml, which is 3.8 times higher than the CG (p <0.001) and 1.6 times than in the group of patients with CKD, IS without PSD (p <0.001). The content of INF-γ in blood serum in the control group was 14.62 (13.04; 16.80) pg/ml, in patients with CKD, IS without PSD 19.87 (15.19; 23.08) pg/ml, which is 1.4 times higher than CG (p <0.001), in patients with CKD, IS with PSD 26.45 (19.06; 32.27) pg/ml, which is 1.8 times higher than CG (p <0.001) and 1.3 times than in the group of patients with CKD, IS without PSD (p <0.001).

The ischemic cascade is triggered after the onset of a stroke, and an immune response is initiated in the damaged tissue. Microglial cells are activated, which, along with other pro-inflammatory mediators, lead to a violation of the integrity and an increase in the permeability of the blood-brain barrier, which contributes to the inflammatory process and aggravates the death of neurons. Neuronal damage can also occur through the humoral pathways due to the release of inflammatory mediators such as INF-γ, TNF-α [9]. Our study revealed a significant increase in the serum levels of INF-γ, TNF-α, IL-1β in elderly patients with CKD during the acute stage of ischemic stroke, while post-stroke depression developed in elderly patients with higher values of these cytokines.

Serum MMP-9 levels in the acute stage of stroke are a possible biomarker for predicting outcomes in patients with IS [10]. In this regard, our study determined the level of fibrosis marker in patients with CKD in the acute stage of IS, depending on the subsequent depression. The level of MMP-9 in CG subjects was 41 (28; 54) pg/ml, in patients with CKD, IS without PSD 117 (90; 144) pg/ml, which is 2.9 times ($p < 0.001$) higher than in CG, in patients with CKD, IS with PSD 159 (123; 194) pg/ml, which is 3.9 times higher than CG ($p < 0.001$) and 1.4 times higher than in the group of patients with CKD, IS without PSD ($p < 0.001$).

Matrix metalloproteinase-9 belongs to the family of zinc-containing endopeptidases capable of destroying extracellular matrix compounds. MMP-9 is localized and released from neurons, astrocytes and microglia, where its expression is regulated by growth factors, cytokines and free radicals. In a study by Che B. et al (2019), the relationship between the level of MMP-9 in patients with acute ischemic stroke and the development of PSD was studied. A multivariate adjusted analysis showed that high serum MMP-9 levels (odds ratio 4.36, 95% CI 2.49–7.65) were an independent predictor of PSD within 3 months of stroke onset [10]. We found that elderly CKD patients with ischemic stroke had higher serum MMP-9 values compared with CG individuals. At the same time, post-stroke depression developed in elderly patients with CKD who had higher MMP-9 values during the acute stage of ischemic stroke, which is consistent with the results of the CATIS multicenter cohort study [10].

Conclusion

Thus, the addition of the determination of the serum level of markers of fibrosis (MMP-9) and immune inflammation (IL-1β, TNF-α, INF-γ) can improve the prediction of the risk of post-stroke depression in elderly patients with chronic kidney disease and ischemic stroke. In addition, the results obtained can help in identifying elderly patients with CKD with IS, who need special attention for the early detection of post-stroke depression.

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