ETHIOPIAN INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH

eISSN: 2349-5715 pISSN: 2349-5707

Volume: 11, Issue 01, Jan-2024 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980

IMMUNOPATHOGENETIC ASPECTS OF ISCHEMIC STROKE

Karimov B.B.

Department of Neurology,

Andijan State Medical Institute Uzbekistan, Andijan

Abstract: Ischemic stroke (IS) remains the most common neurological pathology [1,2] and can manifest itself in the form of malignant ischemic stroke (MIS), leading not only to severe disability of the patient, but also to life-threatening conditions [3,4]. Malignant ischemic stroke is one of the most dangerous manifestations of ischemic stroke, threatening disability of the working population and the likelihood of death without timely treatment tactics. The diagnosis of "Malignant ischemic stroke" can be made no earlier than 12–24 hours; during this time, irreversible changes in the brain may occur in the brain, accompanied by severe swelling, with the threat of subsequent herniation, therefore, the appointment of adequate and timely treatment tactics is necessary as soon as possible [5,6]. Taking into account the peculiarities of the course of the disease, there is a need to search for predictors of IIS. In order to timely predict irreversible consequences, in this literature review we consider modern approaches to diagnosing the malignant course of ischemic stroke. The analysis of literature data allows us to determine some clinical and laboratory predictors of the development of malignant ischemic stroke and methods for assessing the severity of ischemic stroke. Various possibilities for using the studied markers for practical use in the early diagnosis of MIS are considered. Based on literature data, diagnostic possibilities were analyzed with the aim of prescribing timely and adequate therapy before the onset of irreversible changes in the brain.

Key words:Malignant ischemic stroke, predictors of the course of ischemic stroke.

Ischemic stroke continues to be one of the most important medical and social problems. Ways to improve diagnostics and therapeutic methods have been an important research area for many years, and still remain relevant, but cerebral stroke affects from 5.6 to 6.6 million people a year, which in turn leads to death or severe disability of patients. This problem is global and determines the need to develop methods for timely diagnosis [7]. The most effective measures to prevent the severe consequences of ischemic stroke are carried out in the first hours of the disease, the so-called "therapeutic window" - the first 4.5 hours from the onset of stroke [8][9]. Among severe strokes, the most dangerous is massive ischemic stroke (MIS), which is characterized by a volume of ischemia of more than 50% in the middle cerebral artery or ischemia occupying more than ⅓ of the cerebellar hemisphere. MIS can develop in two ways (benign and malignant) [14]. MII can be considered benign if there is no hemispheric edema and dislocation of the midline structures. ZII is a cerebral infarction in which rapidly progressive swelling of the infarct zone occurs, which leads to dislocation of brain structures with the risk of compression of the brain stem and depression of vital functions. MIS in any variant of its course leads to severe neurological deficits and severe disability, but MIS is a threatening lethal outcome in a short time [14]. Neuroimaging criteria for MIS are well known and widely used in daily practice. The most preferred, accessible and widely used neuroimaging method for MIA is spiral computed tomography (SCT). Depending on the location of the lesion, according to the clinical recommendations of the Ministry of Health of the Russian Federation, the following criteria are distinguished: in the seronegative period (the first 6–8 hours from the onset of the disease), computed tomography (CT) is relatively informative, since during this period only indirect signs of massive ischemic stroke, namely compression of the subarachnoid grooves and increased density of the trunk of the middle cerebral artery (MCA). A stroke in the territory of the middle cerebral artery

eISSN: 2349-5715 pISSN: 2349-5707
Volume: 11, Issue 01, Jan-2024 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980

is considered massive when ischemia is detected, occupying more than 50% of this territory. If there is a suspicion of MIS in the cerebellum, a computed tomogram does not reveal specific changes in the first 6–8 hours, so it is necessary to repeat SCT every 12 hours until signs of a massive stroke in the cerebellum are detected (detection of ischemia occupying more than ⅓ of the cerebellar hemisphere). It is known that with a massive stroke there is a high risk of rapid development of edema and dislocation of the brain; to assess the dynamics of these changes, it is recommended to repeat SCT of the brain after 12, 24 and 48 hours. In case of massive ischemic stroke in the territory of the middle cerebral artery, despite the absence of specific indirect signs indicating the possible development of a malignant course, it is necessary to promptly detect compression of the subarachnoid grooves and increased density of the MCA trunk. When massive ischemic stroke is detected on SCT, there are no specific indirect signs indicating the possible development of a malignant course. Within 24 hours from the onset of the disease with a stroke in the middle cerebral artery basin, one can speak of a malignant course of stroke with a transverse dislocation of more than 2 mm; if there is a suspicion of IIS in the cerebellum, to clarify the massive lesion, it is necessary to identify a mass effect on the part of the ischemic hemisphere (compression of the fourth ventricle and/or cisterns of the posterior cranial fossa and/or brain stem). Within 48 hours from the onset of the disease, to confirm the diagnosis of MIS, a transverse dislocation of more than 7 mm must be detected on a computed tomogram. For ZIS in the cerebellum on the second day of the course of the disease, the CT criteria are the same as on the first day: compression of the IV ventricle and/or cisterns of the posterior cranial fossa and/or brain stem. It is noteworthy that regional CT perfusion with the use of a contrast agent, as well as non-contrast, has an important diagnostic value in IS, as it allows one to determine early signs of malignant ischemia, as well as the ratio of viable tissue and irreversible changes in the brain substance. It should be noted that in patients with severe atrophy of the brain substance, according to SCT data, the prognosis for maintaining vital functions is much better. Clinical symptoms are not obligate and can only, with a certain degree of probability, guide the neurologist about the probable malignant type of course. Criteria based on CT and MRI are a reliable diagnostic method only in the presence of a whole set of neuroimaging markers, some of which may be absent in the early stages of the disease. Thus, it becomes obvious the need to search for a biomarker or a system of biomarkers, when determining which it will be possible to judge the type of course of ischemic stroke at the initial stage of development of the disease. In this case, biomarkers must meet certain criteria (high sensitivity and specificity, ability to be released immediately after the occurrence of a stroke, speed of test execution, convenience from a medical and economic point of view). Provided that such “ideal biomarkers” are available, the following algorithm for diagnosing a malignant type of ischemic stroke can be proposed: 1st stage - after assessing the neurological status, 1 or more characteristic symptoms can be identified, which should entail the 2nd stage (mandatory determination of the concentration of these markers in the blood) and the 3rd stage - in order to confirm the diagnosis, a CT or MRI is performed. The result is a reliable diagnosis - “CII”.

At the moment, the possibility of determining the type of course of ischemic stroke using various biomarkers is being actively studied. The difficulties that researchers have in studying this issue arise in large part from the slow penetration of proteins, both glial and neuronal, through the blood-brain barrier after ischemic stroke. In addition, biomarker indicators can increase not only in response to AI, but also in a number of diseases that mimic the nosology being studied. It is known that there is a direct relationship between the speed of determining the type of ischemic stroke and the most favorable outcome of the disease. Next, we will consider an analysis of the results of the effectiveness of biomarkers that help determine the type of ischemic stroke at the moment. Literature

eISSN: 2349-5715 pISSN: 2349-5707
Volume: 11, Issue 01, Jan-2024 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980

data on SII are extremely scarce. Most authors present the results of the effective use of biomarkers to improve the early diagnosis of IS, while many researchers note a correlation between the severity of IS and the values of biomarker indicators.

A literature search has established that one of the most reliable markers of malignant ischemia is the glial neuropeptide S100-b. T.Yu. Shaitanova [2] assessed the significance of the 100-b level depending on the volume of cerebral ischemia. During the development of acute ischemic stroke, the level of S100-b increases in the blood outside the blood-brain barrier. The degree of S100-b elevation is proportional to the volume of ischemia and correlates with clinical outcomes [1]. Monitoring of neuropeptide in blood serum makes it possible to identify respondents for decompressive craniectomy among patients at risk within 12–16 hours from the onset of the disease to the development of clinical deterioration, when the corresponding changes, according to computed tomography, have not yet occurred. Modern automated test systems for the proposed marker allow you to obtain a research result within 18–20 minutes. The diagnosis of the malignant course of IHM was established in two situations: death within the first 7 days due to edema confirmed by neuroimaging or autopsy, or the appearance of temporary signs of axial dislocation (clinical signs, CT). A comparative analysis of immunological disorders in ischemic stroke and arterial hypertension was carried out at the Scientific Center of Neurology of the Russian Academy of Medical Sciences[9]. The phenotypic composition of lymphocytes was studied, and it can be concluded that in patients with ischemic stroke, compared with patients with arterial hypertension, violations of cellular immunity were identified in the form of a quantitative deficiency in the populations of CD3+, CD4+ cells, and an increase in the deficiency of CD8+ cells. When studying humoral immunity, scientists found that patients with stroke had an increased level of IgM and a decrease in the average level of IgG, which indicates a violation in the humoral immunity. At the same time, changes in the level of IgG were multidirectional and did not differ significantly from the average level of the group of patients with arterial hypertension. The general picture of changes in the immune status in patients with acute ischemic stroke is represented by leukocytosis and lymphopenia, signs of immunodeficiency in both cellular and humoral immunity, which, according to researchers, is a predisposing factor to the development of autoimmune disorders in the post-stroke period. However, this research methodology did not include an assessment of humoral immunity, therefore, in our opinion, it is of interest to study the assessment of these immune disorders taking into account the severity of IS [10].

The assessment of the immunological status of patients with acute ischemic stroke was carried out in studies in 2017 by E.E. Molchanova and L.K. Reshetnikova [31]. The authors of the article note that on the 2nd day of the disease in patients, there is an increase in the level of leukocytes in the blood, a decrease in lymphocytes, mature T-lymphocytes (CD3+), T-helper cells (CD4+) and cytotoxic T-lymphocytes (CD8+). Deviations in immune status indicators are more pronounced with increasing severity of neurological symptoms and the size of the infarction. The clinical and immunological study assessed the severity of stroke using the NIHSS scale. With moderate and severe severity, more pronounced lymphopenia is observed with a significant decrease in the level of T-lymphocytes (CD3+), a subpopulation of T-lymphocytes (CD4+), as well as NK cells (CD16+) and cells expressing Il-2 (CD25+). It should be noted that the most appropriate time for screening patients with ischemic stroke is the first day of the disease, since it is immediately necessary to assess the severity of the disease and adjust therapy accordingly, but the proposed method can be used to confirm the diagnosis of IIS on the second day of the disease. The severity of ischemic stroke has been established to depend on the state of free radical processes in platelet membranes and the

eISSN: 2349-5715 pISSN: 2349-5707
Volume: 11, Issue 01, Jan-2024 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980

phospholipid composition of platelet membranes [3]. During the study, the content of cholesterol and phospholipids (LPH, PS, SFM, PC, PEA) was determined. As a result, an increase in phospholipase A2 activity was reliably detected in all patients, which persisted until the 21st day of the disease. Indicators of intermediate and final products of lipid peroxidation (diene conjugates, malondialdehyde, Schiff bases) are also increased in patients with ischemic stroke. The researchers concluded that membrane-destabilizing mechanisms influence the severity of clinical manifestations of ischemic stroke. Accordingly, the more pronounced these changes are, the more severe the disease. In addition, depletion of the antioxidant system was revealed, namely a decrease in the activity of superoxide dismutase, catalase and a decrease in the content of alpha-tocopherol. According to the authors who conducted the study, determination of PL fractions in platelet membranes can be used as a criterion for preliminary assessment of the severity of ischemic stroke. The most striking expression of biochemical changes is in a group of patients with ischemic stroke (increased levels of lipid hydroperoxides, increased ability of lipoproteins to oxidize, as well as a simultaneous decrease in their resistance to oxidation). In these patients, an increase in the level of thiobarbituric acid, which is a secondary product of lipid peroxidation, was noted in the blood serum. Since the most pronounced changes were in patients with ischemic stroke in the acute phase of the disease and patients with multifactorial dyscirculatory encephalopathy compared with milder manifestations of cerebrovascular pathology, we can conclude that there is a direct relationship between the severity of focal changes in brain tissue and the degree of lipoprotein oxidation. This study examined not only ischemic strokes, but also all the most common cerebrovascular accidents. The study highlights the difference between acute and chronic manifestations of cerebrovascular accidents; the severity of ischemic stroke was not taken into account, however, based on the results of the study, it can be assumed that the degree of lipoprotein oxidation may be an indicator of the severity of ischemic stroke, which requires further study.

It is known that vascular autoregulation, lipid metabolism and, as a consequence, the coagulation component of the blood are negatively affected by hyperhomocysteinemia. T.V. Mironenko in his study [4] focuses on the relationship between the level of plasma homocysteine, cholesterol and the level of neurological deficit. Homocysteine inhibits the function of natural anticoagulants (antithrombin-3, C-protein), which adversely affects the course of ischemic stroke and the recovery time of patients. The study revealed a significant increase in homocysteine in the blood to 18.56 μmol/l (taking into account data from the control group with a normal value of 8.46 μmol/l). It was noted that hyperhomocysteinemia was more pronounced in patients with multiple somatic complications, and a more pronounced increase in the concentration of homocysteine in the blood was observed in men, which the authors associate with the presence of factors in the male part of the population that favor an increase in the concentration of homocysteine, namely smoking, alcohol abuse, diet with a high meat content. It has been established that in patients who have suffered an ischemic stroke, there is an increase in the concentration of plasma homocysteine, low- and very low-density lipoprotein cholesterol, and the atherogenic index. If SII is suspected, homocysteine levels and a set of lipid metabolism indicators can be used on the first day of the disease. However, the study did not differentially analyze homocysteine levels in patients with IS and those with comorbid diseases. Thus, in our opinion, such an analysis is promising and the data obtained require further study. Functional recovery was assessed using the modified Rankin scale and the Bartell index. After conducting logistic regression analysis, it was found that for each concentration unit increase in ACE, the probability of a good outcome on the Rankin scale increased by 1.4 times. Analysis by the Kaplan-Meier method revealed a threshold value for alpha-fetoprotein in the blood (2.28 mU/ml), upon reaching which the functional state according to the Rankin scale and Bartell index becomes

eISSN: 2349-5715 pISSN: 2349-5707
Volume: 11, Issue 01, Jan-2024 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980

better. The obtained indicators (ACE more than 1.53 mU/ml) indicate a decrease in the likelihood of death, and an ACE value of more than 2.28 mU/ml predicts the likelihood of good functional recovery in patients with ischemic stroke. However, no distribution was made according to the severity of ischemic stroke. The role of increasing alpha-fetoprotein levels is mainly to improve the ability to recover.[10]

The level of endothelial progenitor cells (EPC) in patients with ischemic stroke is studied by Yu.A. Belova [6]. These are undifferentiated hematopoietic cells that circulate in the blood. Endothelial progenitor cells promote neurogenesis through the release of neuronal growth factors. An increase in these cells in the blood of patients with ischemic stroke is associated with good functional outcome, limitation of cerebral infarct size, and improvement of neurological symptoms[11]. The authors of the study studied the concentration of EPA in patients with ischemic stroke and found a decrease in EPA content, which indicates endothelial dysfunction in such patients, namely, insufficient restoration of damaged endothelium and a slowdown in the formation of new endothelium. The researchers also clarify that a direct relationship was identified between an increase in EPA concentrations and an improvement in the functional state of patients. This study indicates the distribution of recovery capacity after ischemic stroke over time and finds a clear relationship between the phenotype of circulating endothelial progenitor cells and the completeness of functional recovery, but there is no clear indication of the severity of ischemic stroke. The literature search conducted to study the diagnosis of SII does not allow us to create a full-fledged laboratory complex for verifying the diagnosis of SII. This diagnosis is usually established at the advanced clinical stage, and at this stage basic therapy may be ineffective or not fully effective [8]. In this situation, the clinical picture may not be expressed immediately, and even in this case it is impossible to speak with confidence about an ischemic stroke. CT criteria at the onset of the disease may not be indicative, and a combination of nonspecific signs can suggest a malignant course of stroke. As a result, the complex of nonspecific clinical and CT indicators of IIS justifies the need to search for specific markers of this type of stroke.[12]

After reviewing the literature, we identified several studies that seemed most relevant. Based on these studies, we can propose several clinical and laboratory indicators that will help guide a neurologist towards the malignant course of a stroke:

On the first day of the disease, it is necessary to conduct a blood test for peroxidation products (diene conjugates (nmol/mg lipids): 40.7+3.0; Schiff bases (cu fl/mg lipids): 10.1+0.6 ; malondialdehyde (nmol/mg lipids): 3.63+0.2).

Also, on the first day of the disease, it is necessary to determine the level of homocysteine protein: in severe stroke, its concentration in the blood is 20.6 ± 2.2 μmol/l, a set of indicators of lipid metabolism, total cholesterol (mmol/l) - 5.98 ± 2, LDL cholesterol (mmol/l) - 4.21±0.3, HDL cholesterol (mmol/l) - 1.05±0.2; VLDL cholesterol (mmol/l) - 0.46±0.2, TG (mmol/l) - 1.83±0.3, atherogenic index - 3.39±0.23.

On the second day, it is necessary to take blood to analyze indicators of cellular immunity, while the following values will indicate a severe stroke: T-lymphocytes (CD3+) - 45.1 ± 0.79%, T-helper cells (CD4+) - 30.63± 0.73%, T-cytotoxic lymphocytes (CD8+) - 14.25±0.37%, NK cells (CD16+) - 6.88±0.44%.

Thus, these indicators have the greatest specificity, allowing the doctor to rely on them when prescribing therapy. Indicators that, in our opinion, are more suitable for medical practice than others,

eISSN: 2349-5715 pISSN: 2349-5707

Volume: 11, Issue 01, Jan-2024 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980

nevertheless do not have all the features of the "ideal markers" that we discussed above. Therefore, it is necessary to continue the search for new markers or increase the specificity of existing ones. Further research in this area will help in selecting suitable, timely and adequate therapy and, accordingly, will reduce the likelihood of severe disability and death. Probably, the assessment of an integral complex of biomarkers developed from the standpoint of assessing various parts of the pathogenesis of malignant ischemia is promising. It is necessary in the future to highlight the main indicators of the spectrum of biochemical changes in malignant ischemic stroke, in parallel with comparison with other non-invasive methods of early diagnosis of MIS, and also to strive to increase the study cohorts of patients with this type of stroke, in order to increase the level of diagnosis of the disease under study.

REFERENCES:

1. Drapkina O.M., Kontsevaya A.V., Kalinina A.M., Avdeev S.N., Agaltsov M.V., Aleksandrova L.M., et al. Prevention of chronic non-infectious diseases in the Russian Federation. National guidelines 2022. Cardiovascular therapy and prevention. 2022;21(4):3235. https://doi.org/10.15829/1728-8800-2022-3235.
2. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019;139(10):e56-e528. https://doi.org/10.1161/CIR.0000000000000659. Erratum in: Circulation. 2020;141(2):e33. PMID: 30700139.
3. Kuzmenko N.V., Pliss M.G., Tsyrlin V.A., Galagudza M.M. Meta-analysis of the influence of gender and age on the seasonal dynamics of the risk of cerebral stroke. Health risk analysis. 2023;(1):124-136 https://doi.org/10.21668/health.risk/2023.1.12
4. Martsevich S.Yu., Kutishenko N.P., Suvorov A.Yu. and others on behalf of the LIS-2 research working group. Analysis of anamnestic factors and their role in determining the immediate (hospital) prognosis in patients who have suffered a cerebral stroke or transient ischemic attack. Results of the LIS-2 register. Russian Journal of Cardiology. 2015;(6):14-9. https://doi.org/10.15829/1560-4071-2015-6-14-19.
5. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982-3021. https://doi.org/10.1016/j.jacc.2020.11.010. Erratum in: J Am Coll Cardiol. 2021;77(15):1958-1959. PMID: 33309175;PMCID: PMC7755038.
6. Tolpygina S.N., Zagrebelny A.V., Chernysheva M.I., Voronina V.P., Kutishenko N.P., Dmitrieva N.A., et al. Long-term survival of patients who suffered acute cerebrovascular accident in different age groups in the REGION M register. Russian Journal of Cardiology. 2023;28(2):5250. https://doi.org/10.15829/1560-4071-2023-5250.
7. Romain G, Mariet AS, Jooste V, Duloquin G, Thomas Q, Durier J, et al. Long-Term Relative Survival after Stroke: The Dijon Stroke Registry. Neuroepidemiology. 2020;54(6):498-505. https://doi.org/10.1159/000505160
8. Khasanov R.Sh., Shulaev A.V., Mukhamadeev M.F., Dzhumabaev R.A., Mukhamadieva Yu.S., Zagidullin B.I. and others. Improving the provision of medical care to patients with stroke using

eISSN: 2349-5715 pISSN: 2349-5707

Volume: 11, Issue 01, Jan-2024 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980

JCI standards. First results. Journal named after N.V. Sklifosovsky Emergency medical care. 2023;12(1):140-144. https://doi.org/10.23934/2223-9022-2023-12-1-140-144

9. Gabunia N.Yu., Ivanov I.V., Matsytin N.O. Accreditation according to JCL standards of quality and safety of medical activities. Control points. Quality management in medicine. 2021; (4): 2-8. https://doi.org/10.35400/2658-5898-2021-4-2-8
10. Bord S, Sass I, Hayms G, Moskowitz K, Baruch H, Basis F. Involvement and skepticism towards the JCI Accreditation process among hospital's four sector employees: suggestions for cultural change. Isr J Health Policy Res. 2021;10(1):74. https://doi.org/10.1186/s13584-021-00507-4
11. Kulesh A.A. Neuroprotective therapy in the acute period of ischemic stroke. Neurology, neuropsychiatry, psychosomatics. 2021;13(4):94-102. https://doi.org/10.14412/2074-2711-2021-4-94-102
12. Repina L.A., Romanova T.V., Poverennova I.E. Using scales of clinical severity of stroke to determine rehabilitation prognosis. Saratov scientific and medical journal. 2018;14(1):161-164. eLIBRARY ID: 35558240.
13. Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke. 1989;20(7):864-70. https://doi.org/10.1161/01.str.20.7.864
14. Ischemic stroke and transient ischemic attack in adults. Clinical recommendations. Ministry of Health of the Russian Federation, All-Russian Society of Neurologists. 2021