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EARLY DIAGNOSIS AND FORECASTING OF COMPLICATIONS OF HEMORRHAGIC INSULT IN PATIENTS WITH COMORBID FOND DISEASE (REVIEW)

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Abstract: Strokes with rupture of blood vessels in the brain are called hemorrhagic strokes. Despite the fact that hemorrhagic stroke is less common than ischemic stroke, the incidence of disability and mortality from them is significantly higher. Hemorrhagic strokes account for approximately 13% of all strokes. In the USA, the United Kingdom, and Australia, this figure is 8-15%, and in Korea and Japan - 18-24%. Annually, hemorrhagic strokes account for an average of 12-15% per 100,000 population. Also, the probability of hemorrhagic stroke is high in low- and middle-low-income countries and Asian countries. Especially in recent years, the incidence of the disease has become dominant in African and Asian countries, leading to a further deterioration of the country's economic and social situation and premature death. One of the worst and early complications of hemorrhagic stroke is mortality, which is 25-30% in developed countries and 30-48% in developing and low-income countries. Vascular pathologies, cerebral amyloid angiopathy, arterial hypertension, impaired hemoreology, various inflammatory diseases, diabetes mellitus, and other risk factors contribute significantly to the development of hemorrhagic stroke.

Key words: hemorrhagic stroke, biomarkers, hypertension, diabetes mellitus.

Introduction. We have studied a lot of literature and sources on the research topic. Below is a review of some of the literature that has been studied on a global scale and is more relevant and valuable than others. In this literature, the early differential diagnosis of hemorrhagic stroke, the use of new biomarkers in the diagnosis of hemorrhagic stroke, and the conclusions of their analysis are presented. Also, data were analyzed that help predict the outcome of the disease depending on the amount of some biological markers in the acute period of hemorrhagic stroke.18 studies on the systematic interpretation of risk factors and predictors of ischemic and hemorrhagic stroke among adult patients were observed in the period from 2010 to 2022, which were studied in various countries, such as Taiwan, Germany, Sierra Leone, India, Taipei, Ethiopia, Spain, China, Iran, Nigeria, Ghana, Bangladesh, and Pakistan. A total of 23,119 people participated in the research, the size of the research object ranged from 100 to 1,882,930. The average age of the participants varied from one study to another from 43 years (Putaala et al., 2012) to 78 years (Kelly et al., 2022), with age ranges significantly different in different studies, from 16-90 to 60-69 years. The mean age ranged from 43 to 78 years, with standard deviations showing variability in each study population. Ischemic stroke accounted for 45-80.2% of the total stroke, and hemorrhagic stroke - 15.2-55% of the total stroke. It should be noted that the studies covered various risk factors and demographics associated with stroke types, including age, gender, use of antiplatelet agents, and concomitant diseases. A review of the presented studies shows that the age of patients with hemorrhagic and ischemic stroke varies. The age of patients with hemorrhagic stroke ranged from 18 to 90 years (Lakshmi et al., 2021), the average age was 53.4 ± 12.8 years (Owolabi et al., 2018). The oldest age range was 60.4 ± 12.3 years (Riaz et al., 2015), while other studies recorded similar age ranges, including 52.84 ± 12.45 years (Raghuvanshi, 2014) and 55-85 years (Ekeh et al., 2015). In contrast, the age of patients with ischemic stroke ranged from 16 to 45 years (Chen et al., 2021), and the average age was 61.6 ± 13.5 years (Owolabi et al.,

2018). Comparison of these age ranges shows that patients with ischemic stroke are older than patients with hemorrhagic stroke. Analysis of studies consistently identified hypertension as the most important risk factor for ischemic and hemorrhagic strokes. The prevalence of hypertension during these studies is 38.7-94%. Diabetes mellitus and dyslipidemia are most often associated with ischemic stroke, with a prevalence range of 12.4-80% and 12.8-73.36%, respectively. Family history and heart diseases are also important risk factors. Moderately dependent risk factors include smoking, alcohol consumption, obesity, atrial fibrillation, and heart disease. In addition to the fact that smoking and alcohol consumption are associated with both ischemic and hemorrhagic strokes, it is also associated with obesity, which, according to the results of recent studies, has been identified as a risk factor. Less common risk factors include haematological disorders, poor nutrition, physical inactivity, migraines/headaches, mental stress, and brain injuries. The main observations emphasize the significance of hypertension, diabetes mellitus, and dyslipidemia in the risk of stroke [1].

Intravenous tissue-type plasminogen-activating thrombolytic therapy has long been the main pillar of acute ischemic stroke therapy. However, in patients receiving intravenous IV tPA (thrombolytic therapy with plasminogen activator type 4) therapy, there may be a variable response with small sets of some patients with deteriorating outcomes. Diabetes mellitus is a clinically significant and common vascular disease in patients with acute ischemic stroke (AII), which can increase the risk of hemorrhagic transformation after IV tPA therapy. In this brief overview, we summarized the latest achievements in understanding the underlying mechanisms of increased hemorrhagic transformation in patients with AII with DM after IV tPA therapy. Potential precipitating factors are discussed, including more severe impairment of the blood-brain barrier, increased oxidative stress, neuroinflammation and apoptosis, as well as a number of other factors, such as extracellular proteolytic dysfunction and impairment of collateral flow in DM. In addition, several combined approaches to tPA of experimental studies, which can help improve the severity of tPA-induced GT in patients with AII with diabetes mellitus, are also briefly presented. More clinical and experimental studies are needed, aimed at a better understanding of the mechanisms of exacerbation of DM-associated GH after IV tPA therapy in AII, for the development of potential approaches to the management of AII patients with acute DM, protecting against this harmful complication [2].

Patient records were reviewed to determine the presence of comorbidities in all survivors of hemorrhagic and ischemic strokes (n=330) living in the Swedish municipality. A selection of results recorded by patients was used to assess subjective symptoms, functional outcomes, and overall health. Logistic regression models were used to study the relationship between concomitant diseases, residual and subjective symptoms, on the one hand, and functional outcomes and overall health, on the other. Hypertension was observed in 80% of patients, atrial fibrillation in 24%, diabetes mellitus in 28% (with complications in 4%) and hyperlipidemia, most often hypercholesterolemia, in 30%. In addition, obesity was detected and treated in 5.5% and sleep apnea in 3.3%. Dizziness and imbalance were observed in 18% of patients. The most common psychiatric disorders were depression and anxiety. There were several cases of bipolar disorder, but there was no case of a more serious psychiatric disorder such as schizophrenia. Cognitive impairments were observed in 12% of patients. This includes dementia, as well as mild degrees of cognitive impairments that have some impact on everyday life [3].

The main complication of acute hemorrhagic stroke is thrombosis of the deep veins of the lower extremities, in which abnormal coagulation in the deep veins of the lower extremities leads to venous obstruction and impaired blood flow. The thrombus formed in the deep veins can displace and cause pulmonary embolism, forming venous thromboembolism in combination with deep vein thrombosis (DVT), which can significantly affect the patient's condition. The consequences of DVT include pulmonary embolism, post-thrombotic syndrome, and other long-term complications, which seriously affect the quality of life and can lead to death. Risk factors for DVT are divided into primary and secondary categories. Primary factors include genetic and acquired conditions such as antithrombin deficiency, congenital anomalies in fibrinogen, and mutations in coagulation factors such as Leiden factor V and factor II 20210A [4]. Secondary factors include stroke, prolonged bed rest, aging,

immobilization, and malignancy. However, despite the recognition of stroke as a risk factor, the prevention of LEDVT in the treatment of acute hemorrhagic stroke is insufficient, especially in patients receiving such treatment methods as dehydrating agents and interventional therapy to restore vascular permeability. Existing approaches to LEDVT prevention often involve the use of physical methods, such as pharmacological anticoagulants and compression devices. However, these methods have significant drawbacks. Pharmacological agents may increase the risk of bleeding in stroke patients, especially in patients with active bleeding, and physical measures such as early mobilization or pneumatic compression devices may not always be performed due to neurological deficit and impaired mobility of the patient. These problems emphasize the need to develop targeted and effective prevention strategies, taking into account the specifics and risks of patients with acute hemorrhagic stroke [5].

A total of 189 patients (154 ischemic strokes (II) and 35 parenchymal hemorrhagic strokes (PHI)) were hospitalized within 4.5 hours after the onset of the stroke. Glial fibrillar acid protein (GFAP), retinol-binding protein 4 (RBP-4), N-terminal proB type sodium uretic peptide (NT-proNaUP), and endostatin were measured enzyme-linked immunosorbent assay. In patients with IS, the level of RBP-4, NT-proNaUP, and endostatin was higher than in patients with PHI, and the level of GFAP was lower. The best combination of biomarkers for the detection of IS was RBP-4+NT-proNaUP, which made it possible to identify 29.7% of patients with IS with 100% specificity. In the subgroup of patients, where GFAP was measured with a high-sensitivity analysis, RBP-4, NT-proNaUP, and GFAP constituted 51.5% of patients with IS with 100% specificity. In patients with IS, the level of RBP-4, NT-proBNP, and endostatin was higher than in patients with IHS (intracerebral hemorrhagic stroke), and the level of GFAP was lower. The best combination of biomarkers for determining IS was RBP-4+NT-proBNP, which made it possible to identify 29.7% of patients with IS with 100% specificity. In the subgroup of patients in whom GFAP was measured with a high sensitivity analysis, RBP-4, NT-proBNP, and GFAP constituted 51.5% of patients with IS with 100% specificity. With the introduction of stroke mimics, the specificity decreased to 98.4 and 96.8%, respectively. The values of RBP-4 and NT-proBNP showed similar results to the results of traditional IFA [6].

The level of S-100B in blood serum was measured in the prospective, observational, multicenter cohort study BIOSIGNAL in 1749 patients with a series of acute ischemic strokes (average age 72.0 years, 58.3% men) within 24 hours from the onset of symptoms. Subsequent neuroimaging was performed in all patients who received reperfusion therapy to identify symptomatic intracranial hemorrhage or symptomatic brain edema, or who had a score of 4 or less on NHISS and had clinical deterioration. In 46 (2.6%) patients, symptomatic intracranial hemorrhage and in 90 (5.2%) patients, symptomatic cerebral edema developed. After adaptation to established risk factors, it was found that the log10 S-100B level was independently correlated with symptomatic intracranial bleeding (OR 3.41, 95% CI 1.7-6.9, $p = 0.001$) and symptomatic cerebral edema (OR 4.08, 95% CI 2.3-7.1, $p < 0.001$) in multivariate logistic regression models. It was found that the addition of S-100B to the clinical prognostic model increases the AUC (Areas under the curve (AUC) were calculated as an overall discriminatory measure) from 0.72 to 0.75 ($p = 0.001$) in symptomatic intracranial bleeding and from 0.78 to 0.81 ($p < 0.0001$) in symptomatic cerebral edema. The level of S-100B in blood serum, measured within 24 hours after the onset of symptoms, was independently associated with the development of symptomatic intracranial bleeding and symptomatic cerebral edema in patients with acute ischemic stroke. Thus, S-100B can be useful for early prediction of the risk of stroke complications [7].

Another retrospective cross-sectional study included patients with hemorrhagic stroke who were admitted to the emergency department of the Golestan Hospital in Ahvaz in 2022. The research was also approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethics Code: ajums.REC.1401.053). A total of 285 patients with hemorrhagic stroke were assessed, of which 190 were men and 95 were women. The average age of men was significantly higher than that of women ($P = 0.001$). In addition, the incidence of the disease was significantly higher in men and patients aged 60 and older ($P = 0.0001$). Among the most common comorbidities, hypertension

(70.2%), diabetes mellitus (36.1%), inactivity (35.1%), and cardiac ischemia (31.2%) were noted. Anemia with an abnormally low hemoglobin level was present in 76.5% of patients and was associated with the incidence of hemorrhagic stroke (P = 0.0001). In addition, hyperglycemia was observed in 89.47% of patients, which was also associated with hemorrhagic stroke (P = 0.0001). However, other biomarkers did not show a significant correlation (P>0.05). It is noteworthy that thrombocytopenia was significantly associated with a high risk of death (risk level [95% confidence interval CI]: 0.998 [0.996-1], P = 0.03) [8].

In another study, the number of registered patients with hemorrhagic stroke was 33, including 15 men and 18 women. The age of the patients was 31-65 years. The level of molecular markers in the blood serum of the central nervous system (CNS) was measured in the acute phase of stroke (within 1-3 hours after the stroke), on days 7, 14, and 30 after the onset of the disease. The level of candidate molecular markers in blood serum was measured by enzyme-linked immunosorbent assay in the hyper acute period of the central nervous system in patients with hemorrhagic stroke. Neurotrophic brain-derived factor, neuron-specific enolase, total S-100 protein, neurotrophic factor from the glial cell line, vascular endothelial growth factor, sialized carbohydrate antigen, and superoxide dismutase were identified.

Molecular markers were measured using the automatic microplate enzyme immunoassay Immunomat (TM). The control group included 20 volunteers aged 24-58. Changes in the level of the studied molecular markers in the blood serum of patients in the acute period of hemorrhagic stroke (the first 1-3 hours), compared with the control group, revealed a decrease in the level of S100 protein, neurotrophic factor of the glial cell line, vascular endothelial growth factor, superoxide dismutase, syllable carbohydrate antigen, as well as an increase in the level of brain neurotrophic factor and neuronspecific enolase. The stage of acute hemorrhagic stroke (7-14 days), a statistically significant decrease in the neurotrophic factor of the brain (14 days) and an increase in the vascular endothelial growth factor, superoxide dismutase, and sialized carbohydrate antigen were observed. In the subacute period (30 days) of the disease, a significant increase in the level of vascular endothelial growth factor, superoxide dismutase, and sialized carbohydrate antigens was revealed. The dynamics of cullar markers in the patient's blood serum reflects the processes corresponding to the stages of alteration and regeneration of hemorrhagic stroke [10]. The use of neurotrophic and other specific markers contributes to early diagnosis and proper monitoring of the disease.

Conclusion. From the above literature review, it can be understood that the probability of hemorrhagic stroke occurring against other comorbid background and early diagnosis of hemorrhagic stroke, assessment of the course of the disease using various neurotrophic biomarkers remain relevant to this day. Also, the relationship between the size of the hematoma and the number of neurological scales and biomarkers has not been fully covered in studies conducted to date.

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