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Prognostic significance of modern markers of severity and development of complications in acute cerebrovascular diseases

A. I. Gozhenko[1], L. A. Kovalevska[2], O. V. Telyatnikov[3]

[1]Ukrainian Scientific and Research Institute of Transport Medicine, Odesa
[2]Odessa National Medical University, Odesa
[3]Military Medical Clinical Center of the Southern Region, Odesa

Abstract

Recent studies have shown significantly increasing importance of new risk factors such as high levels of homocysteine and C-reactive protein, the presence of thrombophilia markers in the development of stroke. However, information of their relationship in acute defferent types of stroke and acute cardio-vasculares complications caused by stroke, is limited. The study showed that the impact of biomarkers on the stroke severity is age-dependent and hyperhomocysteinemia is play great importance role.

Key words: stroke, homocysteine, hyperhomocysteinemia.

Прогностична значимість сучасних маркерів важкості та розвитку ускладнень при гострих цереброваскулярних захворюваннях

А. І. Гоженко [1], Л. А. Ковалевська [2], О. В. Телятников [3]

[1]Український науково – дослідний інститут медицини транспорту, м. Одеса,
[2]Одеський Національний медичний університет, м. Одеса,
[3]Військово-медичний клінічний центр Південного Регіону, м. Одеса

Дослідження останніх років вірогідно показали зростаюче значення у розвитку інсультів нових факторів ризику, таких як, високі рівні гомоцистеїну, С-реактивного білка, наявність маркерів тромбофілії. Однак, відомості про взаємовідносини даних біомаркерів у гострому періоді ішемічного інсульту, при різних типах інсультів та розвитку гострих серцево – судинних ускладнень на фоні інсульту обмежені. Проведене дослідження показало, що вплив біомаркерів на тяжкість інсульту має вікові особливості і гіпергомоцистеїнемія грає важливу роль.

Ключові слова: ішемічний інсульт, гомоцистеїн, гіпергомоцистеїнемія.

Cerebrovascular diseases, and ischemic stroke, in particular, occupy a leading position in the structure of morbidity, disability and mortality, which determines the urgency of this problem in the present and predetermines the great interest of scientists and clinicians in its solution. Despite the prophylaxis, in the developed countries, the stroke is already in second place among the causes of fatalities, being between cardiac and oncological pathology [1]. Thus, every tenth person dies from a stroke, and only one in every third patient who has a stroke returns to work. According to some authors, a further increase in mortality from a stroke is projected in the future [1, 2].

The stroke is also common in Ukraine: up to 120,000 new cases are registered every year, with 32.7% of stroke patients dying [3]. Particularly relevant is the problem of acute cerebrovascular disorder among different age groups. In Ukraine, among all patients who suffered a stroke, 35.5% of working-age patients, and only 20% of them returned to work [4].

The traditional notion of stroke and cerebrovascular pathology is associated with high blood pressure, hypercholesterolemia, diabetes mellitus, overweight, heart rhythm disorders, hypodynamia, smoking, and the like. [3, 5, 6]. According to the authors, with the influence of these main factors it is possible to link 60% of all cases of ischemic stroke. However, the

large-scale study of MONICA, conducted in 21 countries of the world, has shown that these factors completely do not explain the development of a number of vascular diseases. Therefore, in recent years, the pathogenetic mechanisms of cerebral vascular lesions, and especially the "new" factors of vascular lesions, so-called metabolic risk factors, the identification of which would enable the timely prevention of the development of vascular disasters, are intensively investigated.

Metabolic disorders are traditionally divided into disorders of metabolism of carbohydrates, amino acids, organic compounds, lysosomal diseases of accumulation, and so on. At the same time, the data obtained at the last time show the special role of pathology of exchange of sulfur-containing acids. Among them, the leading position is hyperhomocysteinemia (GHC). Homocysteine (GC) is a sulfur-free amino acid, an intermediate metabolite of methionine and cysteine. The exchange of homocysteine is based on two biochemical processes - remethylation and transsulfation, and the balance between these processes determines the level of homocysteineemia. As coenzymes of these processes are vitamins B1, B6, B12 and folic acid. The biochemical significance of homocysteine is to maintain the endogeneous methionine stock used in the meteliation reactions in the cysteine syngeesis. Cysteine is a potent antioxidant and plays an important role in the formation of disulfide bonds of connective tissue marquise, as well as being the main source of sulfides and important in the metabolism of metals. Alternatively, homocysteine may be irreversibly converted to cysteine and glutathione. Based on a series of clinical and epidemiological randomized trials conducted in different countries of the world, it has been established that GHC is one of the most serious causes of atherogenesis, leading to many potentially fatal pathologies.

Age and gender differences in the level of homocysteine are noted: the minimum level in children, the physiological decline in pregnancy, with age, the level of homocysteine increases; in men is slightly higher than in women. Analyzing the results of the study, the relationship between the age of the patients and the severity of the GHC was established. In older patients, plasma hyperactivity disorder is higher than that of younger patients. These data confirm the results of a series of multicentre studies, according to which 23-62% of the elderly have a deficiency of vitamin B12, folic acid and pyridoxine, which are cofactors of HC [7, 8].

The increase in the level of homocysteine is cytotoxic, especially for endothelial cells, precisely this hyperhomocesteinemia is considered as one of the factors of atherosclerosis (along with the level of cholesterol, LDL, HDL, LDL, fibrinogen). According to clinical

studies, an increase in the concentration of HC in plasma by 5 μmol / L increases the risk of cardiovascular disease and overall mortality in 1.3-1.7 times [3, 4]. According to the recommendations of the American Association of Cardiologists, the concentration of HC in the blood of 10 μmol / L is the boundary level, especially in the presence of concomitant diseases that may cause an increase in the HC content. Among them, decreased excretory renal function, cardiovascular lesions, hypothyroidism, diabetes mellitus, hyperuricemia [9, 10]. The factors that affect the level of GC and increase the likelihood of its content in the blood, include vitamin deficiencies, smoking, alcohol abuse, a diet with high content of meat and cholesterol-containing products. It is also known that the cause of GHC may be hereditary diseases due to deficiency of enzymes involved in its metabolism [5, 11].

According to modern concepts, in addition to physiological functions, homocysteine has a multicomponent pathogenetic effect. It damages tissue structures of the arteries, initiates the release of cytokines, cyclins and other inflammatory mediators. Its accumulation leads to the dilation of the arterial walls, the formation of local defects in the endothelium, which in turn leads to a subsidence on the vascular wall of cholesterol and calcium [12]. Affecting tissue respiration and causing oxidation of low density lipoprotein and other components of the atherosclerotic plaque, homocysteine provokes oxidative stress in endothelial cells [13]. In addition, by inhibiting the enzyme NO synthase, it blocks the synthesis of nitric oxide, which blocks the synthesis of nitric oxide - a powerful endogenous vasodilator [14]. Moreover, a high level of HC promotes platelet aggregation; violates the function of the tissue activator plasminogen; inhibits the function of natural anticoagulants, such as anitrombine III and protein C; stimulates V, X, XII factors of blood coagulation, giving rise to thrombotic enhancement [4, 6, 9]. Taking into account the significant negative influence of GC on the vascular wall and inadequate substantiation of its role precisely at different types of acute cerebrovascular disorders and additional development of other acute vascular catastrophes on the background of the already existing GPMC, the subject of our curiosity was the question of studying the prevalence of GHC in patients with GPMC, and as well as finding out the dependence of concentration changes in HC on the gender and age of patients, which is very relevant and of great scientific interest.

Conducted clinical studies argue that homocysteine is an independent highly informative predictor of cerebrovascular disease. An increase in the level of homocysteine of more than 12 μmol / L (with normose of 4.6-9.9 μmol / L) correlates with an increase in the risk of vascular catastrophes by more than 2-fold [12]. There is evidence that the decrease in homocysteine and the risk of HPMC can be reduced [15, 26].

Depending on the level of homocysteine in the blood, there are several forms of hyperhomocesteinemia (Table 1) [16].

Table 1. Forms of hyperhomocesteinemia (за Lentz S.R. et Haynes W.G., 2004)

Forms of hyperhomocesteinemia	Homocysteine level, μmol / l	The main reasons
Easy	10-30	- heterozygosity for the defective gene cystathion betasintase; - Homozygosity to replace the base of C677T in the 5,10-methylene tetrahydrofolate reductase gene; - Renal insufficiency - Insignificant deficiency of folic acid and vitamin B 12; - Hypothyroidism; - Alcoholism; - Yatrogenic causes (reception of phenytoin, isoniazid, fibratov, levodopa);
Moderate	30-100	- Renal insufficiency - Moderate deficiency B12; - pronounced deficiency of folate;
Heavy	> 100	- Hereditary homocystinuria due to homozygosity due to defective genes of enzymes, biosynthesis of methionine cystathion-β-synthase or 5,10-methylene tetrahydrofolate reductase; - An inherited disorder of utilization of vitamin B12; - Defined vitamin B12 deficiency.

The severe form of homocysteineemia has pronounced clinical manifestations, such as thromboembolic complications, major arterial lesions. However, the data obtained at the last time suggests that moderate and even mild forms of hyperhomocysteinemia are important clinical significance and require therapeutic correction [17 - 22]. It has been established that increasing homocysteine in the blood is an independent factor in the risk of vascular disease and correlation between homocysteine and stroke [22]. Metaanalysis of the performed studies suggests that the increase in homocysteine is an inducer of atherogenesis. According to indicative data, a decrease in the level of homocysteine to 10 μmol / L can prevent or delay the development of cerebrovascular pathology in 15-40% of the population [23].

Particular attention deserves the results of studies of domestic and foreign scientists who showed a gradual increase in the content of homocysteine from the stage of the acute

period of stroke to the consequences [11, 24]. At present, there is no single explanation of this fact in literary sources. It is possible that not only increase homocysteine causes oxidative stress, but vice versa, under conditions of chronic hypoxia, conditions are created for pathological accumulation of homocysteine, possibly due to the exhaustion of antioxidant systems, and thus causes the development of a "vicious circle".

It is believed that homocysteine causes degradation and blockage of the synthesis of prolonged existent peptides, such as collagen, elastin and proteinuricans. It is able to destroy disulfide bridges in proteins, which leads to their structural and functional disorders. Such delayed effects are difficult to assess in relatively short clinical trials, especially in patients with already existing vascular pathology [15, 22, 25].

The development of ischemic stroke is accompanied by changes in the activity of many markers, which include lactate, pyruvate, nitric oxide, homocysteine, lipid peroxidation indexes. But in the literature there are no scientific works where these markers would be studied in a sharp and subacute period of different types of stroke, vascular complications against the background of an existing stroke.

Thus, the aforesaid causes the necessity of studying the role of homocysteine as an important part of the pathogenesis of vascular pathology and, by analyzing other metabolic factors, the determination of the level of homocysteine should be an integral component of the diagnostic complex, especially in patients with an increased risk of developing cardiovascular diseases.

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