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THE ROLE OF HYPERHOMOCYSTEINEMIA IN THE DEVELOPMENT OF COGNITIVE IMPAIRMENT IN CHRONIC CEREBRAL ISCHEMIA

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Summary
Increased levels of C-reactive protein (CRP) and hypercomocysteinemia are considered as independent factors for the development of endothelial damage and atherosclerosis. The sluggish inflammatory process that occurs in the endothelium is usually not associated with infections. The accumulation of homocysteine leads to loosening of the walls of the arteries, the appearance of local defects in the endothelium. People with high homocysteine levels in this group have an increased risk of Alzheimer's disease and cognitive impairment.

Keywords: C-reactive protein, hypercomocysteinemia, cognitive impairment, homocysteine.

РАЗВИТИЕ КОГНИТИВНЫХ НАРУШЕНИЙ ПРИ ХРОНИЧЕСКОМ ИШЕМИЧЕСКОМ ИНСУЛЬТЕ, РОЛЬ ГИПЕРГОМОЦИСТЕИНЕМИИ.

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Резюме
Повышение уровня С-реактивного белка (СРБ) и гипергомоцистеинемия рассматриваются как самостоятельные факторы поражения эндотелия и развития атеросклероза. Вялый воспалительный процесс, протекающий в эндотелии, обычно не связан с инфекциями. Накопление гомоцистеина приводит к расслаблению стенок артерий, появлению местных дефектов эндотелия. Люди с высоким уровнем гомоцистеина в этой группе имеют повышенный риск болезни Альцгеймера и когнитивных нарушений.

Ключевые слова: С-реактивный белок, гипергомоцистеинемия, когнитивные нарушения, гомоцистеин.

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SURUNKALI ISHEMIK INSULTDA KOGNITIV BUZILISHLARNING RIVOJLANISHI, GIPERGOMOTSISTEINEMIYANING ROLI.

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Buxoro davlat tibbiyot instituti

Annotatsiya
C-reaktiv oqsil (CRP) va gipergomosisteinemiya darajasining oshishi endotelial shikastlanish va ateroskleroz rivojlanishining mustaqil omillari sifatida qaraladi. Endoteliyada yuzaga keladigan sust yallig'lanish jarayoni odatda infektsiyalar bilan bog'liq emas. Gomosistein to'planishi arteriyalar devorlarini bo'shashtirishiga, endoteliyada mahalliy nuqsonlarning paydo bo'lishiga olib keladi. Ushbu guruhdagi gomosistein darajasi yuqori bo'lgan odamlarda Altsgeymer kasalligi va kognitiv buzilish xavfi ortadi.

Kalit so'zlari: C-reaktiv oqsil, gipergomosisteinemiya, kognitiv buzilish, Gomosistein.

Relevance
Cerebral ischemia is a neurodegenerative process that causes persistent oxidative damage to brain tissue, suppression of the tissue antioxidant defense system, and significant impairment of memory functions [1]. Factors that aggravate the degree of development of oxidative stress include homocysteine and its autooxidation products, mainly homocysteine acid. The concentration of the total level of homocysteine in the bloodstream increases with the development of neurodegenerative processes, such as Alzheimer's disease and Parkinson's disease [2–4]. Currently, an elevated level of homocysteine is regarded as an independent risk factor for cardiovascular and neurodegenerative diseases [3, 4].
Recent studies have shown that homocysteine is a more informative indicator of the development of cardiovascular diseases than total cholesterol, and is an independent factor in the formation of both stenocclusive lesions of the main arteries [4], deep vein thrombosis [2] and microangiopathy [3], and subsequent cerebrovascular events, especially in patients with coronary artery disease, kidney disease, type 2 diabetes mellitus [8].
In 9.6% of patients with venous thrombosis, of the known risk factors for thrombosis, only hyperhomocysteinemia is detected [17]. According to a number of authors, an increase in the level of homocysteine by only 20-30% can lead to irreversible consequences, including ischemic stroke. An increase in the level of blood

homocysteine by 5 μmol/l from the upper limit of the norm leads to an increase in the risk of atherosclerotic vascular lesions by 60% in men and 80% in women [2]. It is also known that hyperhomocysteinemia accompanies a number of oncological diseases.

Hyperhomocysteinuria and hyperhomocysteinemia are associated with defects in the molecules of cystathionine beta synthase and methylenetetrahydrofolate reductase.

The methylenetetrahydrofolate reductase gene (C677T) is the replacement of cytosine with thymidine at position 677, which leads to the replacement of alanine with valine in the apoprotein of this enzyme. This is the most studied variant of the MTHFR gene polymorphism, in which homocysteine in the blood increases. Defects M5, M10-MTHFR in adulthood are observed in 54% of cases among all thrombophilic disorders and lead to hyperhomocysteinemia of intermediate and medium levels (more than 15 μmol/l). However, according to some data, the association of this mutation in the development of cerebrovascular diseases was noted in 16% of cases [13].

The methylenetetrahydrofolate reductase gene (A1298C) is a variant of the MTHFR gene polymorphism with the replacement of adenine by cytosine at position 1298, which is not accompanied by an increase in the level of homocysteine in the blood. However, the combination of heterozygosity for 677T and 1298C alleles is accompanied by an increase in plasma homocysteine levels, a decrease in folate levels, and a decrease in MTHFR enzyme activity.

Differences in genotypes: The difference between TT and CC MTHFR genotypes results in an average homocysteine difference of 2 μmol/L, which in turn, according to studies, has a 20% difference in the risk of stroke. The independent difference between TT and SS genotypes for stroke is 26% [17].

The TT genotype has a worse prognosis for the development of stroke (compared to CT and SS). The relative risk of stroke with T allele carriage increases by 17% (OR=1.17, 95% CI 1.09-1.26), with the TT genotype the risk of stroke increases by 37% (OR=1.37; 95% CI 1.15-1.64), together with other risk factors, the prognosis worsens to a greater extent (T allele: OR=1.18; 95% CI 1.09-1.29; TT genotype: OR 1.48; 95% CI 1.22-1.8) [10]. The MTP methionine synthase gene (A2756G) - a polymorphism variant with the replacement of arginine by glutamine leads to factor V resistance to activated protein C, and, as a result, to an increase in thrombin formation and fibrin clot resistance, this leads to an uncontrolled blood coagulation process, which increases the risk of acute renal failure and cardiovascular disease.

A decrease in the level of pyridoxine, cyanocobalamin, and folic acid in food causes hyperhomocysteinemia not only in homozygous carriers, but also in people without mutations in the homocysteine metabolism genes (low-protein nutrition leads to

increased homocysteine remethylation pathways and inhibition of transsulfonation reactions) [2]. A significant role in the development of secondary hyperhomocysteinemia is assigned to nutritional factors, since a diet low in vitamins can lead to blockade of the corresponding metabolic pathways. Concomitant factors are lifestyle, various diseases, taking drugs that lead to changes in the concentration of vitamins in blood plasma, changes in enzyme activity, and kidney function [13].

The level of homocysteine in the blood is affected by:

- Smoking - causes a decrease in blood levels of vitamins B6, B12 due to exposure to cyanides contained in cigarette smoke. Each cigarette smoked per day increases the level of homocysteine by 1% in women and by 0.5% in men [15]. Moreover, the highest correlation of hyperhomocysteinemia was found with arterial hypertension and smoking;
- Drinking coffee - caffeine can inhibit methionine synthase. Among men aged 40-42 years who consume more than 6 cups of strong coffee a day, the concentration of homocysteine in the blood is 19% higher than among non-drinkers; in women - by 28%;
- Alcohol abuse - in those suffering from alcoholism, the content of vitamin B6 in blood plasma and folate in erythrocytes is significantly reduced; in addition, ethanol inhibits the activity of methionine synthase in the liver, contributing to an increase in the concentration of homocysteine in the blood plasma;
- Impaired renal function - in patients with chronic renal failure, there is a decrease in creatinine excretion, an increase in folate excretion;
- Protein-rich food increases the level of homocysteine in blood plasma by 10-15% after 6-8 hours, which also explains the higher levels of homocysteine in the evening [15];
- Insufficiency of pyridoxines, cobalamins and folates can be enhanced, for example, by parasitism of Helicobacter pylori, which, in case of low efficacy of oral therapy, requires parenteral administration of drugs, as well as confirmation of microbial parasitism, which makes it difficult to absorb drugs [2].

An increase in homocysteine in the blood is caused by diseases that reduce the absorption of vitamins (gastritis, peptic ulcer, ulcerative colitis, Crohn's disease, celiac disease, enteritis, etc.), as well as accompanied by a large number of dividing cells that consume a huge amount of methyl groups (breast cancer glands, ovaries, pancreas, psoriasis, systemic lupus erythematosus, lymphoblastic leukemia, etc.).

The use of nitrous oxide during general anesthesia leads to temporary hyperhomocysteinemia (inactivates methionine synthase); methotrexate (inhibits dihydrofolate reductase); omeprazole, metformin, H2 receptor antagonists (inhibit

the absorption of cobalamin); isoniazid, theophylline (inhibit pyridoxalkinase); cyclosporine, fibrates (impair kidney function); diuretics (reduce glomerular filtration); methylprednisolone (reduces the concentration of vitamin B6); sulfonamides (cause folic acid deficiency); estrogen-containing contraceptives, anticonvulsants (violate the metabolism of folic acid in the liver); drugs L-DOPA (increase the methylation process). There is also a temporary increase in homocysteine after the use of high doses of nicotinic acid [16], prolonged physical activity, which is sometimes associated with the diet followed by athletes [3, 5]. The use of d-penicylamine in the treatment, n-acetylcysteine (disulfide replacement), adenosine analogs (inhibit adhomocysteine hydrolase), estrogen (in menopause), simvastatin (to the end unknown mechanism) leads to a decrease in plasma homocysteine. In 20% of patients with ischemic stroke, there is also a decrease in the concentration of homocysteine in the blood plasma.

According to the results of various studies [10], the determination of the lower value of homocysteine in the blood is unambiguous (5 μmol/l). It is believed that before puberty, homocysteine concentration levels in boys and girls are approximately the same (about 5 μmol / l). During puberty, the amino acid level rises to 6-7 μmol/l, in adults - 5-15 μmol/l (absolute norm). In modern literature, the presence of a metabolite in the blood is defined as an independent risk factor for thrombovascular disease when the level of circulating homocysteine in the blood exceeds 8-10 μmol/l, and the level of homocysteine 10-12 μmol/l in individuals with concomitant diseases should be qualified as moderate hyperhomocysteinemia. Based on numerous studies proving the relationship between an increase in homocysteine and the development of certain diseases, a concentration of about 10 μmol / l (relative norm) in adults has been recognized by the World Health Organization as borderline in the diagnosis of diseases, i.e. above this indicator in people at risk, it can be argued that the disease is in question [3, 5, 50]. It is believed that after ingestion of a protein meal, the level of homocysteine reaches a peak in the blood after 6-8 hours, and then slowly (half-life is 3-4 hours) is excreted from the plasma. Therefore, blood sampling should be carried out on an empty stomach approximately after a 12-hour fast [12].

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