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# Homocysteine as a Marker of Cerebrovascular Diseases

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**Abstract:** Hyperhomocysteinemia is a common and modifiable risk factor for cerebrovascular disease. The literature data presented in the review confirms the contributing role of hyperhomocysteinemia in the development of pathology of the cerebrovascular system, as well as the importance of taking into account, in this regard, disorders of homocysteine metabolism when carrying out primary and secondary prevention of athero- and thrombovascular complications. This involves leading a healthy lifestyle with limiting foods that increase homocysteine levels, adhering to the principles of a balanced diet with increased consumption of plant-based foods rich in folic acid and B vitamins. It is also advisable to control homocysteine levels in patients who are taking medications that affect vitamin folate status.

**Key words:** hyperhomocysteinemia, dyscirculatory encephalopathy, cognitive impairment, brain damage, vascular dementia.

**Relevance.** A few years ago, the World Health Organization recognized a homocysteine concentration of more than 10 µmol/l (relative norm) in adults as borderline for the diagnosis of diseases, which made it possible to identify the disease in question in people at risk [3]. According to modern concepts, homocysteine is a non-proteinogenic amino acid with one methylene group [26,29]. Homocysteine is synthesized from methionine by removing the terminal methyl group. It is important to note that homocysteine does not come from food, is not a vitamin, and is not part of the proteins of the human body. Normally, homocysteine is synthesized from methionine in a multistep process. First, methionine is alkylated with adenosine triphosphate to form S-adenosylmethionine [3]. Then, with the help of the enzyme cytinosyl-5-methyltransferase, S-adenosylmethionine transfers its methyl group to cytosine in deoxyribonucleic acid, forming adenosylhomocysteine. The enzyme adenosylhomocysteinase then catalyzes the hydrolysis of this product to form homocysteine. Normally, due to the dynamic processes of remethylation and transsulfuration, homocysteine levels remain stable. Purpose of the study: analysis of scientific literature on homocysteine metabolism and its effect on human health, with an emphasis on renal and cerebrovascular diseases. Many studies have confirmed that for the functioning of the processes of remethylation and transsulfuration, the body must have sufficient levels of vitamins B1 (riboflavin), B6 (pyridoxine), B12 (cyanocobalamin) and folic acid, which act as coenzymes [3,7,11,15]. Consequently, pathological accumulation of homocysteine can result from both genetically determined defects in the enzymes involved in the above reactions and a lack of vitamins B1, B6, B12 and folic acid in the diet. In addition, an increase in homocysteine in the blood serum can be observed with long-term use of drugs such as omeprazole, methylprednisolone, theophylline, metformin, cyclosporine A, isoniazid, sulfonamides, fibrates, nicotinic acid, H2-receptor antagonists, levodopa, carbamazepine, hydrogen pump blockers, aminophylline, estrogen-containing

contraceptives, cytostatics, nitrous oxide and anticonvulsants. These drugs affect homocysteine metabolic pathways that require the participation of vitamins as cofactors or enzyme substrates. Some studies show that protein-rich foods increase serum homocysteine levels by 10–15% after 6–8 hours, which explains higher homocysteine levels in the evening [6]. The accumulated information on homocysteine metabolism was summarized by international expert W. Herrmann in 2006 and published in the journal Clinical Laboratory [17]. There are the following degrees of hyperhomocysteinemia: mild (15-30 μmol/l), moderate (31-100 μmol/l) and severe (>100 μmol/l). There is evidence that among people in older age groups, moderate hyperhomocysteinemia is detected in 40% of cases [13]. Hyperhomocysthenia can be detected in individuals with thyroid dysfunction, chronic hyperglycemia, hematological diseases, psoriasis, smoking, coffee abuse, etc. For example, each cigarette smoked per day increases homocysteine levels by 1% in women and by 0.5% in men [3, 4]. In individuals who drink more than six cups of coffee per day, homocysteine levels are 2-3 μmol/L higher than in non-coffee drinkers, since caffeine can inhibit methionine synthase [9]. As some researchers note, among men aged 40-42 years who drink more than six cups of strong coffee per day, the concentration of homocysteine in the blood is 19% higher than among non-drinkers; in women – by 28% [9]. Currently, high levels of homocysteine in blood plasma are considered as a risk factor for the development of both atherosclerotic and thrombogenic vascular damage. In the publication by A.M. Pristrom described in detail the problem of hyperhomocysteinemia and the role of homocysteine in the development of cardiovascular diseases (CVD) [9]. The problem of genetic disorders in the conversion of folic acid into its active form - 5-methyltetrahydrofolate and the possibility of correcting folate status has been raised [9]. The study of the pathogenetic mechanisms of cerebrovascular diseases, including hyperhomocysteinemia, with the aim of developing methods for pharmacological correction of these conditions is currently of increasing interest.

Studies have confirmed that an increase in homocysteine concentration is an independent risk factor for the development of cerebrovascular diseases [16,13,14,16,14]. Thus, with an increase in plasma homocysteine level by 2.5 mmol/l, an increase in the risk of developing acute cerebrovascular accident by 20% was noted [6,7]. It was found that an increase in blood homocysteine levels by 5 μmol/L from the upper limit of normal leads to an increase in the risk of atherosclerotic arterial disease, and the risk was higher in women [17]. It is equally important to note that folate deficiency is accompanied by a number of mental disorders. Meta-analysis by J.H. Park et al demonstrated the secondary protective effects of folic acid and B vitamins on stroke prevention [22]. Obviously, the functions of neuroglia require rapid cellular renewal, which is impossible under conditions of folate deficiency. The severity and duration of depression were found to be significantly associated with serum folate concentrations [2, 7]. Noteworthy are the results of the work of R. Cui et al., conducted as part of the JACC study, where the level of homocysteine in the blood serum was examined in 39,242 people aged 40 - 79 years from 1988 to 1990 [13]. It has been established that patients with high serum homocysteine levels have a significantly increased risk of mortality in ischemic stroke. During the 10-year follow-up period, 444 deaths from general CVD were recorded, including 310 cases from cerebral stroke (hemorrhagic and ischemic stroke, 131 and 101, respectively) [13]. Observational studies have demonstrated that elevated homocysteine levels lead to a threefold increase in the risk of developing cerebrovascular diseases and the value of homocysteine is important for determining the prognosis of patients with an established diagnosis of CVD [15,19]. Another study showed that people with serum homocysteine levels ≥16 μmol/L have an increased risk of developing CVD, and a decrease in its level by 25% was associated with a decrease in the risk of

stroke by 19% [22]. The American College of Cardiology/American Heart Association practice guidelines emphasize that homocysteine levels ≥12.1 μmol/L are associated with a twofold increased risk of atherosclerotic vascular disease, including stroke, independent of traditional risk factors [18]. Homocysteine levels ≤10 μmol/L are considered to have a low risk of cerebral stroke [4]. It is assumed that hyperhomocysteinemia increases the risk of developing Alzheimer's disease (Aloise Alzheimer, 1864 - 1915) and senile dementia [3, 9]. According to a number of authors [3, 6], an increase in homocysteine levels by only 20–30% can lead to irreversible consequences, including ischemic stroke. A.Yu. Polushin et al analyzed the relationship between the volume of brain damage and homocysteine concentration in 43 patients in the acute period of ischemic stroke [8]. It was shown that in the subgroup of patients with the atherothrombotic subtype of ischemic stroke, 6 (42.9%) patients had blood homocysteine levels twice as high as the reference values (average value 25.97 μmol/l) [8]. The average volume of the lesion was 37.7±4.3 cm3, which was statistically significantly different from the values of patients without hyperhomocysteinemia. This group also revealed a strong positive correlation between homocysteine concentration and the volume of the ischemic lesion. In this study, among patients with the cardioembolic subtype, three had plasma homocysteine levels greater than 20 μmol/L; in 5 (31.25%) patients, homocysteine levels ranged between 10 and 19 μmol/l (average 15.6 μmol/l) [8]. A strong positive correlation was also found between serum homocysteine levels and the extent of brain damage. The authors concluded that patients with the atherothrombotic subtype of stroke with concomitant hyperhomocysteinemia have more extensive damage to the brain [8]. In another study, homocysteine levels correlated with both the severity of atherosclerosis and blood cholesterol levels [4]. In addition, in the noted study, general and cerebral atherosclerosis in patients with hyperhomocysteinemia was recorded significantly more often, and the level of cholesterol in the blood plasma was higher than in the group with normal levels of homocysteine in the blood plasma [4]. Thus, hyperhomocysteinemia influenced the risk factors for cerebrovascular disease—hypercholesterolemia and cerebral atherosclerosis. Recent cohort studies also support the role of hyperhomocysteinemia as a factor influencing the severity of ischemic stroke [12]. High homocysteine levels are associated with carotid atherosclerosis in both elderly and young patients. Thus, in the publication of S.K. Evtushenko and D.A. Filimonov, dedicated to the role of homocysteine in the development of ischemic strokes in young people, noted that in an 8-year-old boy with anomalies in the development of the bone skeleton, death occurred as a result of a stroke [2]. An autopsy of the deceased revealed a sharp narrowing of the lumen of the carotid arteries due to many atherosclerotic plaques - “this was atherosclerosis, which can be found in elderly people” [2].

Homocysteine damages the tissue structures of the arteries, initiating the release of pro-inflammatory cytokines, cyclins and other inflammatory mediators. In addition, homocysteine inhibits glutathione peroxidase and thus stimulates endothelial cell proliferation [17]. At the same time, homocysteine inhibits the production of nitric oxide by endothelial cells and platelets and increases the formation of reactive oxygen species due to the release of arachidonic acid from platelets. As a rule, the result of atherothrombotic events in the cerebrovascular system is chronic cerebral ischemia [7,8]. As noted, lower values of thinking speed and short-term verbal memory were observed in patients with plasma homocysteine levels more than 14 μmol/l [13]. It is assumed that an increase in blood homocysteine levels is one of the risk factors for the progression of mild cognitive impairment to dementia. The effect of hyperhomocysteinemia on clinical-neuropsychological and laboratory-instrumental parameters in patients suffering from Alzheimer's disease, vascular and mixed (vascular-neurodegenerative) dementia and non-

dementia cognitive disorders was studied in the work of V.Yu. Lobzina, I.V. Litvinenko and A.Yu. Emelina [4]. The authors examined 110 patients with varying degrees of severity of cognitive impairment due to Alzheimer's disease, cerebrovascular disease, or a combination of both [4]. It was found that an increase in homocysteine levels correlated with a decrease in the total score on the Mini-Mental State Examination scale, the clock drawing technique, and the Frontal Assessment Batter, symbol-digit test, Mattis dementia scale. At the same time, the connection between the severity of disorders of higher cortical functions and hyperhomocysteinemia was also confirmed by the presence of an average strength of positive correlation with the score on the Clinical Dementia Rating scale. Patients with hyperhomocysteinemia were also characterized by metabolic disturbances in the posterior cingulate cortex, but their severity did not differ from patients with normal levels of the amino acid under study [4]. The mentioned study noted that hyperhomocysteinemia can also have an independent effect on the neurodegenerative process and the progression of cognitive disorders due to the activation of demethylation, oxidative stress with the formation of thiolactone compounds and, as a consequence, loss of neuronal plasticity, which is manifested by earlier metabolic disorders in the anterior cingulate areas [4]. It has now been shown that homocysteine may be a potential biomarker for assessing the effectiveness of dual and single antiplatelet therapy in patients with ischemic stroke or transient ischemic attack [26].

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