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Hyperhomocysteinemia And Pathogenetic Mechanisms Of Ischemic Stroke

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ABSTRACT

The article is intended to give basic information and the role of homocysteine in the human body. The amino acid homocysteine is a product of methionine demethylation. When the level of homocysteine increases, it damages the tissue structures of the arteries, initiating the release of cytokines, cyclins and other inflammatory mediators. Its accumulation leads to loosening of the arterial walls, the formation of local defects in the endothelium, which, in turn, leads to the deposition of cholesterol and calcium on the vascular wall. Hyperhomocysteinemia as a consequence of impaired homocysteine metabolism is considered an independent risk factor for stroke in humans. The role of neuroprotective therapy in interrupting or slowing down the sequence of damaging biochemical and molecular processes that can cause irreversible ischemic brain damage is shown.

KEYWORDS

Homocysteine, hyperhomocysteinemia, ischemic stroke, HC metabolism, neuroprotection.

INTRODUCTION

History of the study of homocysteine. In 1932, an outstanding American biochemist and Nobel Prize winner Vincent Du Vigno synthesized a new, previously unknown amino

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acid by acting on methionine with sulfuric acid. In 1933, a clinical case of dementia, lens dystopia, and skeletal malformations in an 8-year-old boy was described. The child died from an ischemic stroke. On autopsy, pathologist Tracy Mallory revealed a sharp narrowing of the lumen of the carotid arteries due to a variety of atherosclerotic plaques - "it was atherosclerosis that can be found in the elderly." It is noteworthy that in 1965 the nephew of this child was diagnosed with hyperhomocysteinuria. Later, in 1968, a case of homocysteinuria in a 2-month-old child was described, caused by a defect in methionine synthetase. Autopsy revealed atherosclerotic lesions of all large arteries. At the same time, population studies related to hyperhomocysteinemia began to be carried out. Homocysteine is a sulfur-containing amino acid synthesized endogenously from methionine. HC is not a vitamin and is not part of the proteins of the human body. The exchange of homocysteine is based on two biochemical constants - remethylation and transsulfonation, it is the balance between these mechanisms that determines its level. For the functioning of both pathways, a sufficient concentration of vitamins B1, B6, B12 and folic acid is required, which act as coenzymes in the reactions of remthylation and transsulfonation [4].

Pathological accumulation of HC can be caused by 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. When studying polymorphism for the methylenetetrahydrofolate reductase gene, it was found that 10–16% of the population is homozygous for this variant, and this is characterized by an increased content of homocysteine. Deficiencies in B vitamins are also fairly common, leading to increased levels of homocysteinemia. Thus, the prerequisites are created for the widespread prevalence of hyperhomocysteinemia in the population [2].

With hyperhomocysteinemia, the concentration of low and very low density lipoproteins increases, the production of endothelial relaxing factor and sulfated glycosaminoglycans decreases, and serine proteases are activated. All this leads to the processes of damage to endotheliocytes and elastic membrane. The synthesis of prostacyclin decreases, the growth of smooth muscle cells of the vascular wall and the proliferation of the endothelium are stimulated, the synthesis of thrombomodulin, an endothelial protein, is inhibited, without which the process of activation of natural anticoagulants by thrombin is disrupted. At the same time, the V factor of blood coagulation is modified, as a result, it becomes insensitive to the action of protein C. The above processes lead to an additional increase in the coagulation properties of blood [4].

Thus, the pathogenetic role of hyperhomocysteinemia is twofold: it consists in damage to the endothelium and associated early atherogenesis, as well as in an increased tendency to develop venous and arterial thrombosis.

In numerous population studies, the lower homocysteine level is usually determined rather unambiguously (5mkmol / l), but the upper limit usually varies between 10 and 20 μmol/l - depending on age, gender, ethnic group and characteristics of folate consumption. Depending on the level of homocysteine in the blood, several forms of hyperhomocysteinemia are distinguished:

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severe HHC (> 100 µmol / L), moderate HHC (30-100 µmol / L), mild HHC (10-30 µmol / L).

The results of numerous studies have revealed a clear correlation between the level of homocysteine and the risk of developing cerebrovascular diseases, especially ischemic stroke. A meta-analysis of published works shows that an increase in homocysteine levels is an inducer of atherogenesis. According to rough estimates, a decrease in the level of homocysteine to 10 µmol / L could prevent or delay the development of cerebrovascular pathology in 15–40% of the population. A 25% increase in homocysteine levels (i.e., 3 µmol/L) is associated with a 19% increased risk of stroke. Similar results were obtained from a retrospective analysis of the case histories of 16,849 patients. When reviewing other works, only 7% did not reveal a clear relationship between hyperhomocysteinemia and IS mortality [2].

Hyperhomocysteinemia of moderate severity is found in 42% of patients with cerebrovascular disorders under the age of 50. It has been proven that in men aged 40-50 years, the risk of stroke increases by 4.1 times with moderate hyperhomocysteinemia. And severe hyperhomocysteinemia is the cause of more than half of all cases of ischemic stroke, myocardial infarction and pulmonary embolism in patients under 30 years of age. A number of population studies have shown that hyperhomocysteinemia is recorded in children with ischemic stroke 4.4 times more often than in the control group [1].

The research results of prof. I.S. Zozuli and co-authors. A gradual increase in plasma homocysteine content from the acute period of stroke to the stage of consequences has been shown. Similar results were obtained in the works of Recep Aygal1, Dilcan Kotan (2008), an increase in the concentration of G. in plasma and cerebrospinal fluid from the acute stage of stroke to the consequences was revealed [3].

At the moment, there is no single explanation for this fact in the literary sources. It is possible that not only an increase in the level of homocysteine causes oxidative stress, but also vice versa, i.e. in conditions of chronic hypoxia, conditions are created for the pathological accumulation of homocysteine, possibly due to the depletion of antioxidant systems, thereby leading to the emergence of a "vicious circle".

Thus, the analysis of foreign and domestic literature indicates that impaired homocysteine metabolism is an important factor influencing the onset and course of ischemic stroke, especially in young people. Examination of patients with ischemic stroke, as well as its prevention in young people, in addition to the standard set of diagnostic measures, should include an expanded study of the state of the hemostasis system, immunological tests, to identify and cause hyperhomocysteinemia. High homocysteine levels require therapeutic correction, appropriate diets and medications in order to prevent ischemic stroke in young people.

The amino acid homocysteine (HC), which is a product of methionine demethylation, has attracted particular interest of researchers for about half a century. HC is a sulfur-containing amino acid synthesized endogenously from methionine [13]. HC metabolism is based on two biochemical constants - remethylation and transsulfonation; it is the balance between these mechanisms that determines its level. For the functioning of both

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pathways, a sufficient concentration of vitamins B1, B6, B12 and folic acid is required, which act as coenzymes in the reactions of remethylation and transsulfonation [13, 17]. In blood plasma, free (reduced) HC is present in small amounts (1-2%). About 20% is in an oxidized state, predominantly in the form of a mixed disulfide of cysteinyl homocysteine and homocysteine.

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme involved in plasma GC metabolism, catalyzing the conversion of 5-, 10-methyltetrahydrofolate to 5-methyltetrahydrofolate [30]. HC is an important intermediate in methionine metabolism and causes excessive production of reactive oxygen species [18]. During stress, levels of reactive oxygen species can be dramatically increased, leading to damage to cellular structures. For example, an increased level of HC can induce cell apoptosis. It has been shown that an increase in plasma HC levels is associated with an increased risk of ischemic stroke (IS) [22, 29]. The MTHFR gene is localized on chromosome 1 p36.3, and to date, more than 40 point mutations or point nucleotide polymorphisms have been found in the identified MTHFR gene (Nndle NucLeotide Po (tornybtb, SNPs) [10]. Of these, the most significant mutations associated with IS are C677T (^ 1801133) and A1298C (^ 1801131) [24]. The most frequently studied genetic variant, which demonstrates the strongest association with elevated HC levels, is cytosine substitution (C) to thymine (T) at position 677 of the MTHFR gene (^ 1801133) [11,16]. This mis-sense mutation results in approximately 70% and 35% decrease in the normal enzymatic activity of MTHFR in carriers of the TT and CT genotypes, respectively [21]. Variant A1298C leads to the substitution of glutamate (Ig) for alanine (A1a) at codon 429 in the S-adenosylmethionine regulatory domain of the MTHFR protein [24]. The genetic variant of MTHFR C677T can lead to increased plasma HC levels and, thus, to an increased risk of developing IS [36], which has been confirmed in other studies [22,28]. associated with IS are C677T (^ 1801133) and A1298C (^ 1801131) [44, 66]. The most frequently studied genetic variant, which demonstrates the strongest association with elevated HC levels, is the substitution of cytosine (C) for thymine (T) in position 677 of the MTHFR gene (^ 1801133) [11,16]. This mis-sense mutation results in approximately 70% and 35% decrease in the normal enzymatic activity of MTHFR in carriers of the TT and CT genotypes, respectively [21]. Variant A1298C leads to the substitution of glutamate (Ig) for alanine (A1a) at codon 429 in the S-adenosylmethionine regulatory domain of the MTHFR protein [24]. The genetic variant of MTHFR C677T can lead to increased plasma HC levels and, thus, to an increased risk of developing IS [16], which has been confirmed in other studies [22,28]. associated with IS are C677T (^ 1801133) and A1298C (^ 1801131) [14]. The most frequently studied genetic variant, which demonstrates the strongest association with elevated HC levels, is the substitution of cytosine (C) for thymine (T) in position 677 of the MTHFR gene (^ 1801133) [11,16]. This mis-sense mutation results in approximately 70% and 35% decrease in the normal enzymatic activity of MTHFR in carriers of the TT and CT genotypes, respectively [21]. Variant A1298C leads to the substitution of glutamate (Ig) for alanine (A1a) at codon 429 in the S-adenosylmethionine regulatory domain of the MTHFR protein [24]. The genetic variant of MTHFR C677T can lead to increased plasma HC levels and, thus, to an increased risk of developing IS [5], which has

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been confirmed in other studies [22]. The most frequently studied genetic variant, which demonstrates the strongest association with elevated HC levels, is the substitution of cytosine (C) for thymine (T) at position 677 of the MTHFR gene (^ 1801133) [11,16]. This mis-sense mutation results in approximately 70% and 35% decrease in the normal enzymatic activity of MTHFR in carriers of the TT and CT genotypes, respectively [21]. Variant A1298C leads to the substitution of glutamate (Ig) for alanine (A1a) at codon 429 in the S-adenosylmethionine regulatory domain of the MTHFR protein [24]. The genetic variant of MTHFR C677T can lead to increased plasma HC levels and, thus, to an increased risk of developing IS [25], which has been confirmed in other studies [22]. The most frequently studied genetic variant, which demonstrates the strongest association with elevated HC levels, is the substitution of cytosine (C) for thymine (T) at position 677 of the MTHFR gene (^ 1801133) [11]. This mis-sense mutation results in approximately 70% and 35% decrease in the normal enzymatic activity of MTHFR in carriers of the TT and CT genotypes, respectively [21]. Variant A1298C leads to the substitution of glutamate (Ig) for alanine (A1a) at codon 429 in the S-adenosylmethionine regulatory domain of the MTHFR protein [24,25]. The genetic variant of MTHFR C677T can lead to increased plasma HC levels and, thus, to an increased risk of developing IS [36,40], which has been confirmed in other studies [22]. is a substitution of cytosine (C) for thymine (T) at position 677 of the MTHFR gene (^ 1801133) [11,16]. This mis-sense mutation results in approximately 70% and 35% decrease in the normal enzymatic activity of MTHFR in carriers of the TT and CT genotypes, respectively [21]. Variant A1298C leads to the substitution of glutamate (Ig) for alanine (A1a) at codon 429 in the S-adenosylmethionine regulatory domain of the MTHFR protein. The genetic variant of MTHFR C677T can lead to increased plasma HC levels and, thus, to an increased risk of developing IS [36,40], which has been confirmed in other studies [22]. is a substitution of cytosine (C) for thymine (T) at position 677 of the MTHFR gene (^ 1801133) [11,16]. This mis-sense mutation results in approximately 70% and 35% decrease in the normal enzymatic activity of MTHFR in carriers of the TT and CT genotypes, respectively [21]. Variant A1298C leads to the substitution of glutamate (Ig) for alanine (A1a) at codon 429 in the S-adenosylmethionine regulatory domain of the MTHFR protein [24]. The genetic variant of MTHFR C677T can lead to increased plasma HC levels and, thus, to an increased risk of developing IS [19], which has been confirmed in other studies [22]. Variant A1298C leads to the substitution of glutamate (Ig) for alanine (A1a) at codon 429 in the S-adenosylmethionine regulatory domain of the MTHFR protein [24]. The genetic variant of MTHFR C677T can lead to increased plasma HC levels and, thus, to an increased risk of developing IS [19], which has been confirmed in other studies [22]. Variant A1298C leads to the substitution of glutamate (Ig) for alanine (A1a) at codon 429 in the S-adenosylmethionine regulatory domain of the MTHFR protein [24]. The genetic variant of MTHFR C677T can lead to increased plasma HC levels and, thus, to an increased risk of developing IS [11], which has been confirmed in other studies [22].

According to modern concepts, besides the physiological function, HC has a multicomponent pathogenetic effect. It damages the tissue structures of the arteries, initiating the release of cytokines, cyclins and

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other inflammatory mediators [9,17,29]. Its accumulation leads to loosening of the artery walls, the formation of local defects in the endothelium, which, in turn, leads to sedimentation on the vascular wall cholesterol and calcium [19]. HC is believed to increase the risk of thrombus formation by inducing endothelial damage in the venous and arterial vascular system [29]. HC is a potential procoagulant due to its ability to inhibit antithrombin III, protein C and activate factors V and XII, which is of particular importance for the development of atherothrombotic and cardiogenic ischemic strokes [20,27]. Acting on tissue respiration and causing oxidation of low density lipoproteins and other components of atherosclerotic plaque, HC provokes oxidative stress in endothelial cells [18]. In addition, by inhibiting the enzyme NO synthetase, it blocks the synthesis of nitric oxide, a powerful endogenous vasodilator [14].

The normal HC content in the blood is 5-15 µmol / L. During life, the average level increases by 3-5 µmol/L. This is due to a deterioration in kidney function and other physiological reactions that affect metabolic processes in the body. The level of HC in the blood depends on gender and age: it is higher in men and in older age groups. At the age of 40–42 years in men and women, the difference in the concentration of HC is approximately 2 µmol / L, with average values of about 11 and 9 µmol/L, respectively [17]. There are observations that in patients over 55 years of age the level of HC in the blood is higher than in patients of younger age [10].

A meta-analysis of published studies shows that an increase in HC levels is an inducer of atherogenesis. According to rough estimates, a decrease in HC levels to 10 µmol/L could prevent or delay the development of cerebrovascular pathology in 15-40% of the population [23]. Also, with long-term follow-up for 641 patients in 13 countries for 4.5 years, it was shown that a high level of HC leads to a threefold increase in the risk of developing cerebrovascular diseases and the value of HC is important for determining the prognosis of patients with an already established diagnosis of cardiovascular disease (CVD) [21].

As has been confirmed by many studies, even mild hyperhomocysteinemia (HHC) can increase the risk of developing IS, probably due to the pleiotropic biochemical properties of HC and its effect on atherosclerotic vascular changes [14]. In fact, HC suppresses the production of NO by endothelial cells and platelets and increases the formation of reactive oxygen species due to the release of arachidonic acid from platelets. It also inhibits glutathione peroxidase and thus stimulates endothelial cell proliferation [23].

Elevated plasma HC levels have been associated with the risk of IS in observational studies [25]. Moreover, experimental studies show that an increase in total HC levels aggravates vascular disease [19]. In a study by Han L. et al. [22], which included 5,935 patients, the average HHC levels were 13.60 µmol / L in the group as a whole, in men - 15.96 µmol/L, in women - 11.70 µmol / L. Men had higher levels of HHC and a higher prevalence of HHC than women in different age groups ($p < 0.0001$). It has also been noted that the extent and prevalence of HHC increases with age. IS patients were also further divided into 2 groups based on HC levels (<15 and £ 15 µmol / L). The authors found that after 2.7 years of follow-up, the frequency of IS was 3.82% in patients with essential hypertension, 6, 18% in

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the HHC group (HC £ 15 µmol / L) and 2.84% in the control group (HC <15 µmol / L). The RR (95% CI) for IS induced by HHC were 2.18 (1.65-2.89), 2.40 (1.56-3.67) and 2.73 (1.83-4.08) for all participants, men and women, respectively. Another study surveyed 5,665 middle-aged UK residents evidence linking HC levels with the development of cerebral stroke. With long-term (over 12.8 years) observation, it turned out that the level of HC was higher in the group of 141 men who developed IS than in the control group of the same age. The difference in the relative risk of stroke was 2.8 between individuals with upper and lower quartiles of HZ level. Severe HHC is the cause of more than half of all cases of IS in patients under 30 years of age [48]. HHC of moderate severity is found in 42% of patients with cerebrovascular disorders under the age of 55 years [14].

Case-control studies have shown that elevated HC levels are primarily a risk factor for lacunar stroke [28,30]. In the case of the lacunar subtype, heterogeneity within this subtype has been shown with the strongest associations in these cases with small vessel disease and multiple lacunar infarctions and leukoaraiosis on magnetic resonance imaging (MRI) [23]. Other studies have shown that HC increases the risk of developing both IS associated with small vessel disease and atherothrombotic strokes [28, 41]. High HC levels are associated with carotid atherosclerosis in both elderly and young patients [8,28]. It has been shown that an increase in HC concentration is associated with a more rapid progression of stenosing lesions of large arteries and an increase in the size of atherosclerotic plaques [19].

It has now been shown that elevated HC levels are associated with secondary vascular events and increased mortality after stroke [19]. According to Shi Z. et al. [11], who observed 3,799 patients with the first IS for 48 months and determined the level of HC on the first day after hospitalization, 233 (6.1%) patients died. After adjusting for age, smoking, diabetes, and other CVD risk factors, patients with the highest quartile of HHC (> 18.6 µmol / L) had a 1.61-fold increased risk of death (RR 1.61; 95% CI, 1. 03-2.53) compared with patients with a low quartile of HHC (^ 10 µmol/L). Further analysis of the subgroups showed that this correlation was significant only when atherothrombotic subtype (RR 1.80, 95% CI, 1.05-3.07), but was not significant in stroke with small vessel involvement (RR 0.80, 95% CI, 0.30-2.12). The risk of death associated with stroke was 2.27 times higher in patients in the third quartile of HHC (RR 2.27, 95% CI, 1.06-4.86) and 2.15 times higher in patients in the fourth quartile. (RR 2.15, 95% CI, 1.01-4.63) than those with the lowest quartile of HHC. R. Ssh et al. [21] also reported that patients with the highest HHC quartile had a significantly increased risk of mortality in IS (RR 4.35, 95% CI, 1.12-16.9) compared with patients with the lowest quartile.

The basis of AI therapy is two directions: reperfusion and neuronal protection. Reperfusion is associated with the restoration of blood flow in the ischemic zone. Neuronal protection is implemented at the cellular level and is aimed at preventing the death of weakly or almost non-functioning, but still viable neurons located around the heart attack (zone of "ischemic penumbra"). The main methods of reperfusion are thrombolysis. The main methods of neuroprotection include restoration and maintenance of homeostasis; drug protection of the brain and non-drug methods such as

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hyperbaric oxygenation, cerebral hypothermia. Antithrombotic drugs, including anticoagulants and antiplatelet agents, are required for all patients who have undergone IS or TIA [26]. To date, acetylsalicylic acid (ASA) is the "gold standard" in the prevention of cardiovascular diseases after noncardioembolic IS and TIA [6].

Persons with identified HHC are advised to follow a diet high in B vitamins (green vegetables, legumes, lean meat, fish, curd restriction), take courses of folic acid and B vitamins, and also control the level of HC, coagulogram, lipid profile 2 times in year. In the acute and subacute stages of IS, when HHC is detected, in addition to conventional therapy, it is recommended to take folic acid and preparations containing high doses of B vitamins, which is a component of secondary prevention of stroke [7].

A recent large-scale study on primary prevention of stroke in China (China Stroke Primary Prevention Trial, CSPPT), which recruited only hypertensive patients, demonstrated a positive effect in reducing the risk of stroke with the use of B vitamins [27]. A secondary analysis in the Vitamins to Prevent Stroke study (VITATOPS) found a borderline effect of treatment with B vitamins in patients with lacunar stroke (hazard ratio 0.80 (95% confidence interval [CI] 0.67-0.96), while MRI The result of therapy was associated with a decrease in the progression of white matter lesion volume in patients with severe white matter lesions [12].

Thus, an increased level of HC is observed in IS, being partly a modifiable risk factor. The pathogenesis of HHC is currently attracting great attention from researchers because early intervention can be beneficial for patients and prevent HHC-induced additional cell damage. A simple blood test that can easily detect HHC can be helpful in screening patients with CVD. The issue of HHC therapy remains controversial and requires further in-depth study.

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