World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-21, April 2023
ISSN: 2749-3644

ELEVATED HOMOCYSTEIN LEVELS AS A RISK FACTOR FOR THE DISEASE IN CEREBRAL ISCHEMIA

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Article history:

Received: February 11th 2023
Accepted: March 11th 2023
Published: April 12th 2023

Abstract:

The amino acid homocysteine (HC), which is a product of methionine demethylation, has been of particular interest to researchers for about half a century. HC is a sulfur-containing amino acid synthesized endogenously from methionine. The article describes the role of homocysteine and the problem of hyperhomocysteinemia in the development of cognitive impairment in cerebrovascular diseases and chronic ischemic ischemia.

Keywords: hyperhomocysteinemia, homocystein, remethylation, vascular wall, neurotransmitter monoamines

Stroke is one of the leading causes of death in any population, and its prevention is a key strategy to reduce mortality and morbidity. According to a number of authors [Carmel, R. 2021], an increase in homocysteine levels by only 20–30% can lead to irreversible consequences, including ischemic stroke.

HC metabolism is based on two biochemical constants - remethylation and transsulfonation, it is the balance between these mechanisms that determines its level [1]. The functioning of both pathways requires a sufficient concentration of vitamins B1, B6, B12 and folic acid, which act as coenzymes in remethylation and transsulfonation reactions [2]. In blood plasma, free (reduced) HC is present in small amounts (1-2%). Approximately 20% is in the oxidized state, predominantly as a mixed disulfide of cysteinyl homocysteine and homocystin. About 80% of HC binds to plasma proteins, mainly albumin, forming a disulfide bond with cysteine.

According to modern concepts, in addition to the physiological function, HC has a multicomponent pathogenetic effect. It damages the tissue structures of the arteries, initiating the release of cytokines, cyclins and other inflammatory mediators [3]. Its accumulation leads to loosening of the walls of the arteries, the formation of local defects in the endothelium, which, in turn, leads to deposition of cholesterol and calcium on the vascular wall [4]. It is believed that HC increases the risk of thrombosis by inducing endothelial damage in the venous and arterial vascular system [5]. 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 [6,7]. By affecting tissue respiration and causing oxidation of low-density lipoproteins and other components of atherosclerotic plaque, HC provokes oxidative stress in endothelial cells [8]. In addition, by inhibiting the enzyme NO synthetase, it blocks the synthesis of nitric oxide, a powerful endogenous vasodilator [9].

Homocysteine can also be metabolized to S-adenosylhomocysteine, which has neurotoxicity, inhibition of the methylation reaction, and consequently inhibition of the metabolism of neurotransmitter monoamines, methylation of proteins and phospholipids. In the relationship between homocysteine and vascular pathology, cerebrovascular disease occupies a special place. As a result of the meta-analysis, a 2.5-fold increase in the risk of developing cerebrovascular diseases with hyperhomocysteinemia was proved [10]. In another study, moderate hyperhomocysteinemia was detected in 42% of patients with cerebrovascular disease under the age of 55 [11].

The Rotterdam study observed an association between plasma homocysteine levels and neuropsychological outcomes. Lower values of the speed of thinking and short term verbal memory were observed in patients with plasma homocysteine levels of more than 14 μmol /L [10]. In an interim report from the Framingham study Offspring showed that - cognitive impairment was related to plasma homocysteine levels in older adults among the elderly. In patients with initially higher levels of homocysteine, dementia developed significantly more often after several years, in contrast to patients with initially normal levels. In the NAME study, which studied the relationship between nutrition, age, and mnestic disorders in older people, higher concentrations of homocysteine were also found in patients with dementia [12].

In the Hordaland study , plasma homocysteine levels decreased in direct proportion to cognitive ability

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Available Online at: https://www.scholarexpress.net
Volume-21, April 2023
ISSN: 2749-3644

over a 6-year follow-up period [9]. Approximately the same results were obtained in other multicenter studies: it was shown that homocysteine and its determinants (vitamin B12 , folate) can affect cognitive impairment and the course of Alzheimer's disease (AD) [6]. Vitamin B deficiency and hyperhomocysteinemia are common in the elderly and are associated with the incidence of asthma [7].

The main mechanism for the development of dementia in hyperhomocysteinemia is the toxic effect of homocysteine on the vascular wall, which explains the development of cognitive disorders in cerebrovascular pathology. Thus, the progression of vascular or mixed dementia can be slowed down by taking folic acid, vitamin B_{12} and vitamin B_6 . In a recent placebo-controlled trial with vitamin support (folic acid 0.8 mg, B_{12} 0.5 mg, B_6 20 mg/day) for 24 months, Smith AD ef al . [15] observed a slowdown in the progression of cerebral atrophy according to magnetic resonance imaging. In patients receiving therapy, the rate of atrophy was 29.6% slower. In another two-year placebo-controlled study in carotid stenosis, the use of 5 mg of folic acid and 250 mg of vitamin B_6 caused a slight, subtle improvement in hemodynamic parameters according to magnetic resonance angiography [16]. Patients who have had a stroke, in the presence of concomitant hyperhomocysteinemia , have more extensive ischemic damage to the medulla [4].

Recently, the range of studies begun in the 1990s [1] and devoted to the study of the role of neurotrophic factors in the formation of the fetal nervous system has been expanded. It has been established that such neurotrophins as the - neurotrophic factor of the brain (brain-derived neurotrophic factor - BDNF) and nerve growth factor (nerve growth factor , NGF), are involved in the vital - processes of growth and differentiation of neurons in the central nervous system (CNS) and peripheral nervous system of the developing fetus [2–4]. It is most likely that the mechanism of action of these neurotrophic factors is related to their influence on angiogenesis and cell growth, survival, and maturation of neurons [2, 5].

The expression and secretion of neuregulin NRG1 by stromal decidual cells and its role in the paracrine regulation of survival, differentiation, and provision of adequate invasion of cells of the extravillous trophoblast due to the activation of signaling pathways leading to suppression of apoptosis [23].

Many studies have confirmed that for the functioning of the processes of remethylation and transsulfonation , the body must have a sufficient content of vitamins B1 (riboflavin), B6 (pyridoxine), B12 (cyanocobalamin) and folic acid, which act as coenzymes [3,7,11,35]. Therefore, 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 can lead to pathological accumulation of homocysteine . In addition, an increase in serum homocysteine can be observed with long-term use of drugs such as omeprazole , methylprednisolone , theophylline, metformin, cyclosporin A , isoniazid, sulfonamides, fibrates , nicotinic acid, H2 receptor antagonists, levodopa , carbamazepine , hydrogen pump blockers , aminofillin, estrogen-containing contraceptives , cytostatics, nitrous oxide and anticonvulsants. These drugs affect homocysteine metabolism pathways that require the participation of vitamins as cofactors or enzyme substrates. Some studies show that protein-rich food increases serum homocysteine levels by 10-15% after 6-8 hours, which explains the higher levels of homocysteine in the evening [6]. The accumulated knowledge on the metabolism of homocysteine was summarized by the international expert W. Herrmann in 2006 and published in the journal Clinical laboratory [17].

Despite the fact that prenatal HHC is the cause of deep functional disorders in the CNS of the offspring, as evidenced by the works published earlier by us [2], as well as by other domestic and foreign researchers [7], it is not completely clear what causes these disorders. and to what extent they are due to changes in the functional state of the placenta. It is important that HHC in the mother is accompanied, as noted in the above experimental studies, by an increase in the content of homocysteine in the blood of newborn animals. This indicates that homocysteine, which is formed in an increased concentration due to a violation of its metabolism, overcomes the fetoplacental and, possibly, the blood-brain barrier by simple diffusion or by binding to a specific receptor [8]. The authors of the studies carried out in this direction believe that the cause of the observed changes is the increased sensitivity of the cells of the nervous system to excitotoxic and oxidative damage induced by HHC, as judged on the basis of the obtained data on the suppression of the function of NMDA glutamate receptors [9], inhibition of the activity of antioxidant enzymes and a decrease in the content of low molecular weight antioxidants [1], a decrease in the survival of neurons with increased generation of reactive oxygen species [12], changes

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in the expression of neurotrophic factors BDNF and NGF [3], as well as proteins S-100B, GFAP and NCAM, which are markers of neuronal maturation and astrocytes . The above neurochemical disorders were found in the offspring of rats that underwent prenatal HHC on the 1st [3, 4] and 10–12th days of postnatal - development [7] and were combined with subsequent impairments of their cognitive functions on 45th [7] and 75th days of life [3]. The role of oxidative stress in HHC-induced disorders in the development of the nervous system and cognitive function of the offspring is also confirmed by the fact that they can be eliminated by administering melatonin and some short peptides with pronounced antioxidant properties to animals during pregnancy [2, 3].

Hyperhomocysteinemia is a common and modifiable risk factor for nephro- and cerebrovascular diseases. The literature data presented in the review confirm the contributing role of hyperhomocysteinemia in the development of pathology of the kidneys and cerebrovascular system, as well as the importance of taking into account, in this regard, disorders of homocysteine metabolism during primary and secondary prevention of athero- and thrombovascular complications. This involves maintaining a healthy lifestyle with the restriction of products that increase the level of homocysteine, adherence to the principles of a balanced diet with an increased intake of plant products rich in folic acid and B vitamins. It is also advisable to control the level of homocysteine in patients who take drugs that affect vitamin - folate status .

The most significant processes that reflect the functional state of the placenta, which are affected by HHC, include apoptosis. It has been established that homocysteine induces the processes of apoptosis and cell death in the trophoblast [15] and in the fetal brain [26], its proapoptotic effect is suppressed by the administration of folates [7].

According to the literature data, the mechanism of activation of apoptosis during HHC in various cell types can be carried out both "externally", through the interaction of extracellular signals with cell surface receptors [18], and "internally", associated with the destruction of mitochondria under the influence of oxidative stress, accompanied by the release of cytochrome C into the cytoplasm [19], which was noted, in particular, when homocysteine was exposed - to trophoblast cells [44, 45]. The mechanism of the proapoptotic action of homocysteine, according to most researchers, is due to the oxidative stress induced by it, since as a result of the action of homocysteine and its metabolic products, a significant amount of reactive oxygen species is formed that triggers the mechanism of cell death. It is interesting that neurotrophins expressed in the placenta , including BDNF [9], as well as melatonin, which inhibits both the external receptor and internal mitochondrial pathways of apoptosis in the trophoblast , have an antiapoptotic effect [20].

CONCLUSION. A few years ago, the World Health Organization recognized a homocysteine concentration of more than 10 μmol /l (relative norm) in adults as a borderline in the diagnosis of diseases, which made it possible to identify the desired disease in people at risk [3]. According to modern concepts, homocysteine is a nonproteinogenic 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 multi- step process. First, methionine is alkylated with adenosine triphosphate to form S- adenosylmethionine . [3]. Then, using the enzyme cytinosyl-5-methyltransferase, S- adenosylmethionine transfers its methyl group to cytosine to 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 transsulfonation , the level of homocysteine remains stable.

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Volume-21, April 2023
ISSN: 2749-3644

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