Homocysteine, Atherothrombosis, and Stroke

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Abstract. The main causes of mortality worldwide are infarct and stroke. Atherosclerosis is found to be an etiologic factor. That is why attention is focused on the detection of new risk factors of atherosclerosis and its correction. Hyperhomocysteinemia is a relatively new, independent and modified risk factor for ischemic stroke and other atherosclerotic vascular diseases. Hyperhomocysteinemia is observed in less than 5% of the population. The direct association between hyperhomocysteinemia and atherothrombosis development is confirmed. Nowadays, hyperhomocysteinemia's correction may be included into the prevention of stroke as well as the treatment of diabetes and hypertension. Its level may be decreased by life style correction and B group vitamins intake.

Keywords: hyperhomocysteinemia, atherothrombosis, stroke.

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INTRODUCTION

Infarctions, stroke and other vascular diseases are of high incidence worldwide. Atherosclerosis frequently is found to be an etiologic factor for the above-mentioned pathologies. The cause of the problem is occlusion of blood vessels by fat deposits, called atheromata. Young and old, males and females, rich and poor, almost anyone is prone to developing this condition. According to WHO statistical data 7.2 million people died of cardiac diseases and 4.62 million of stroke in 1996. Over 32 million cases of atherothrombosis are detected yearly all over the world. Obviously, atherosclerosis can be considered as our time epidemic [1–3]. Although classic atherosclerosis risk factors are determined, as well as atherosclerosis correction and control offered, it remains one of the leading mortality causes worldwide [4–6]. Nowadays, we are neither able to name those risk factors that exactly cause development of atherosclerosis, nor those only contributing to the progression of the latter. Moreover, it is not clear whether all risk factors have been discovered and why in some cases of myocardial infarction and stroke not a single known risk factor can be detected. Answers to all these questions still must be found. In this article we would like to analyze relatively new but quite well-researched risk factor – hyperhomocysteinemia.

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WHAT IS HOMOCYSTEINE?

Butz de Vigneaud was the first to describe homocysteine (Hcy) in 1932, which since that time has become the main topic of many researches concerning hyperhomocysteinemia. In 1962 Hcy was found in the urine of a mentally retarded child, and some years later cysteine beta - synthase genetic defect was linked to homocysteinuria cause [8]. Patients with this particular genetic defect appeared to develop hypercysteinemia, early-onset atherosclerosis, and frequent thromboembolism [9]. In 1969 McCully described several pathological findings of ahomocysteinuria patients: vascular smooth muscle cell proliferation, progressive arterial stenosis, and haemostatic changes. Significant homocysteinuria is found in patients with Hcy genetic defect while moderate serum levels of Hcy and its metabolites are accepted as independent risk factors for ischemic stroke and other atherosclerotic vascular diseases [10–12]. Population-based epidemiology studies confirmed the direct association between moderate homocysteinemia and complicated pregnancies, some neuro-psychotic diseases and congenital abnormalities.

Hcy is an intermediate product of methionine metabolism. In human organism Hcy is metabolised through two major pathways: transsulphuration (cofactor is B12) and re-methylation (B12 and folic acid). Enzyme defects, vitamin deficiency as well as medications can not only affect Hcy metabolism but also impair its level.

Not all the factors equally affect Hcy level. Table 1 represents the effects of some medications, clinical conditions, as well as genetic factors.

Table 1. **Effect of some factors on Hcy level**

Factors	Effects
Genetic factors	
homozygote cystathionine beta-synthase defect	significant hyperhomocysteinemia
homozygote methylen-tetra-hydrofolate reductase defect	significant hyperhomocysteinemia
cobalamin mutations	significant hyperhomocysteinemia
Down syndrome	decreased Hcy
Lifestyle factors	
vitamin intake	decreased Hcy
smoking	mild hyperhomocysteinemia
overuse of coffee	mild hyperhomocysteinemia
ethanol overuse	mild hyperhomocysteinemia
physical activity	decreased Hcy
Clinical conditions	
folates, B12, B6 deficiency	moderate hyperhomocysteinemia
kidney insufficiency	moderate hyperhomocysteinemia
hypothyroidism	moderate hyperhomocysteinemia
Medications	
folate antogonists (methotrexate)	mild hyperhomocysteinemia
antiepileptic medications	mild hyperhomocysteinemia
aminothiol (acetylcysteine)	decreased Hcy
contraceptives	decreased Hcy

HOMOCYSTEINE AND ATHEROTHROMBOSIS

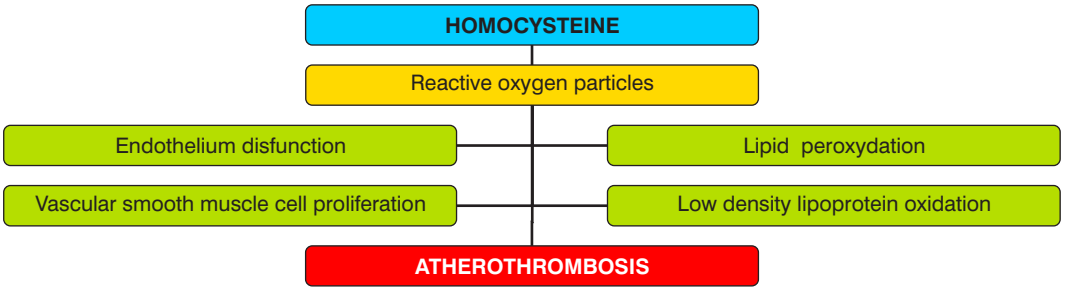
Healthy vascular endothelium is known to obtain certain features which naturally protect a human organism from atherothrombosis and its consequences. To start with, vascular tone is controlled by maintaining the balance of vasoactive mediators. It is mainly provided by nitric oxide (NO) [11], which is synthesized from L-arginine being converted into L-citrulline. NO provides vasodilatation by inhibiting vascular smooth muscle contraction. It also enhances endothelium antithrombotic function by inhibiting platelet aggregation, leukocyte adhesion, monocyte haemotaxis, and smooth muscle cell proliferation. NO bioactivity is significantly decreased in patients with atherothrombosis [12]. Another important function of healthy endothelium is to provide thromboresistance. It "builds" a mechanical barrier which prevents direct contact between blood elements and such subendothelial elements as von Willebrand factor, fibronectin, and collagen, causing platelet adhesion and aggregation. Hyperhomocysteinemia impairs endothelium functions on different levels by decreasing NO synthesis, increasing vascular oxidative injury, and enhancing vascular smooth muscle cell proliferation [15]. Hcy also increases tissue factor expression, decreases heparan sulfate and thrombomodulin production, leading to endothelium antithrombotic function alteration and thrombosis.

Many studies conducted on hyperhomocysteinemia as an early atherosclerosis risk factor demonstrated such typical vascular changes as fibrous plaques and inner elastic membrane damage [16]. Negative influence of Hcy on vascular endothelium cells, by affecting NO and coagulation cells, has been proved experimentally [17–18].

HOMOCYSTEINE AND STROKE

Hyperhomocysteinemia is observed in less than 5% of the population and 50% of stroke patients [19]. Approximately in 30% of stroke patients Hcy serum level is 1.5 times higher compared to healthy individuals of similar age and gender [20]. Moreover, stroke patients with hyperhomocysteinemia more frequently develop cerebral microangiopathy and multiple infarctions compared to patients with normal Hcy serum level [21]. It can be explained by presence of beta-amyloid in Hcy neurotoxic processes. Taking into account that atherotrombosis is a major ischemic stroke risk factor, constituting up to 50% of cases [23–25], many researches have been focused on Hcy as atherothrombotic stroke risk factor. Reliable association between Hcy and ischemic stroke has been noted in 5 prospective studies [11, 12, 26–28], though failed to be confirmed in 2 [29, 30]. Association between Hcy and other stroke risk factors such as diabetes and hypertension is rather unreliable, thus increased Hcy serum level is accepted as stroke independent risk factor [26, 31].

Hyperhomocysteinemia also affects intima media thickness of carotid vessels. Consequently, asymptomatic patients with moderately high Hcy level appear to have increased carotid intima media thickness compared to individuals with normal Hcy level [32].



Picture 1. **Hcy and atherothrombosis**

CAN HOMOCYSTEINE LEVEL BE MODIFIED?

Frequently hyperhomocysteinemia is a condition with multifactorial etiology. Thus, having detected increased Hcy level it is also essential to identify the possible causes. Sometimes Hcy serum level can be normalized by life style correction solely. It is acknowledged that smoking cessation improves lipid profile, lowers thrombotic tendencies and endothelium damage, as well as enhances insulin tissue sensitivity [33]. Some of these effects directly depend on improvement of Hcy metabolism. Dietary correction can also favorably influence Hcy metabolism [34]. Although some hyperhomocysteinemia causes such as diseases and enzyme defects can not be corrected, Hcy level is decreased by life style correction and vitamin intake. There have been conducted many studies on folates, B12 and B6 vitamins as Hcy level regulators [35–42]. Even some genetically predisposed Hcy metabolism impairments can be partially or totally modified by high doses of vitamins [43–45]. Furthermore, a combination of folate and B group vitamins is more effective in lowering Hcy level than folic acid monotherapy.

CONCLUSIONS

Hyperhomocysteinemia is a modified, multifactorial risk factor for stroke associated with premature atherosclerosis, early stroke, and infarction. Vitamin supplementation decreases or even normalizes plasma homocysteine concentrations in most cases. The use of pills containing low dose B vitamins is definitely cheap and may help prevent acute vascular episodes. Nowadays, detection of hyperhomocysteinuria and its correction may be included into the primary and secondary prevention of stroke, as well as to individual approach to every patient [46].

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HOMOCISTEINAS, ATEROTROMBOZĖ IR INSULTAS

Santrauka

Tik 2/3 visų simptomatinės aterotrombozės atvejų galima susieti su žinomais vaskuliarinių ligų rizikos veiksniais. 1/3 aterotrombozės atvejų pasireiškimo priežasčių lieka nežinomos. Kadangi aterosklerozės klinikinės formos, tokios kaip infarktas ir insultas, mirtinų ligų sąraše užima pirmąją vietą pasaulyje, šiandien daug dėmesio skiriama naujiems rizikos veiksniams ir jų korekcijos galimybei ištirti. Vidutinė hiperhomocisteinemija nustatoma maždaug 5% populiacijos. Homocisteinas yra nepriklausomas ir modifikuojamas rizikos veiksnys. Ankstyvoji aterosklerozė, kuri siejama su hiperhomocisteinemija, gali ilgai progresuoti asimptomatiškai ir komplikuotis dėl trombozės. Laiku atlikta hiperhomocisteinemijos korekcija gali būti tiek pat svarbi vaskuliarinių ligų profilaktikoje, kaip ir hipertenzijos bei cukrinio diabeto gydymas.

Raktažodžiai: aterotrombozė, insultas, hiperhomocisteinemija.