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HYPERHOMOCYSTEINEMIA: A RISK FACTOR FOR CARDIOVASCULAR DISEASE

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Summary. *Cardiovascular and peripheral vascular disease are the major cause of morbidity and mortality in general population today. Hyperhomocysteinemia, a new independent risk factor for atherosclerotic vascular disease, has been described in the last ten years. Moderate hyperhomocysteinemia occurs in 5-7% of general population, and is associated in the third and fourth deceny of life with premature coronary disease, stroke, arterial and venous thromboembolism. An increased level of homocysteine could be treated with folic acid. This short review describes the impact of hyperhomocysteinemia on cardiovascular morbidity, and an up-to-date prevention and treatment.*

Key words: *Hyperhomocysteinemia, coronary heart disease, stroke, venous thromboembolism, risk factor*

Introduction

In 1969, McCully reported autopsy evidence of extensive arterial thrombosis and atherosclerosis in two children with elevated plasma homocysteine and homocystinuria (1). On the basis of this observation he proposed that hyperhomocysteinemia can cause atherosclerotic vascular disease. However, only 20 years later interest in hyperhomocysteinemia has been renewed. The recent upsurge in interest for hyperhomocysteinemia has been generated by the evidence that people with homocysteine concentrations in the upper level of "normal" have an increased risk for atherosclerotic cardiovascular disease. Although severe hyperhomocysteinemia is rare, mild hyperhomocysteinemia occurs in 5-7% of the general population (2,3). These patients are asymptomatic until third or fourth decade of life when premature coronary artery disease, stroke, arterial and venous thrombosis develop. In previous studies major attention for atherosclerotic disease was paid to the disturbed lipid metabolism. However, recent epidemiological studies have demonstrated that mild hyperhomocysteinemia is an independent risk factor for atherosclerosis in the coronary, cerebral, and peripheral vasculature (4,5).

Hyperhomocysteinemia and atherosclerotic cardiovascular disease

An abundant epidemiological evidence from more than 20 case-control and cross-sectional studies has validated the relation between hyperhomocysteinemia and atherosclerosis (5,6). Clarke et al. measured homocysteine concentrations after methionine loading in a cohort of men with premature vascular disease and demonstrated that 42% of patients with cerebrovascular disease, 28% of patients with peripheral vascular disease, and 30% of patients with coronary artery disease had hyperhomocysteinemia (4). The relative risk of coronary artery disease in patients with hyperhomocysteinemia was approximately 24 times that in control.

Several studies have demonstrated an association between an increased homocysteine level and coronary sclerosis (7-10), or myocardial infarction (11,12). In the Physicians Health Study, 14.916 male physicians without initial homocysteine measurement and were prospectively followed for an average of five years (12). The authors estimated that 7% of 271 observed myocardial infarctions could be attributed to hyperhomocysteinemia. Men with plasma homocysteine 12% above the upper limit of normal had approximately a threefold increase in the risk for myocardial infarction.

The prevalence of carotid artery stenosis increases with increasing plasma concentrations of homocysteine (13). The risk of carotid stenosis was increased even at lower plasma concentrations of homocysteine, between 11.4 and 14.3 μmol/L, that had previously considered to be normal. There was a graded, rather than a threshold, relation between plasma homocysteine and the risk of carotid stenosis (13).

Although venous thromoboembolism represents about 50% of vascular complications of hyperhomocysteinemia, this problem has attracted less interest. In a

review article from 1997, 10 papers, and 1200 patients, from 1991 to 1996 have been analyzed (14). Eight of these ten studies have demonstrated an association. An analysis on 269 patients, with a first episode of venous thrombosis, has demonstrated that homocysteine is the risk factor for deep vein thrombosis, more important in women than in men, and increasing with age (15).

Hyperhomocysteinemia and atherosclerosis in renal failure

Cardiovascular morbidity and mortality in end-stage renal failure is increased (16). Several reports have demonstrated an association between hyperhomocysteinemia and atherosclerosis in chronic renal failure patients, including grafted patients (17-20). Several factors were suggested responsible for hyperhomocysteinemia in chronic renal failure, including deficient intake or deranged metabolism of vitamins (folic acid, B6, B12) (21-24), decreased renal clearance of homocysteine (25,26), accumulation of toxic metabolites inhibiting homocysteine metabolism (27), and mutation of gene of the methylenetetrahydrofolate reductase (28,29).

Genetic defects in homocysteine metabolism

Homocysteine is a sulfur containing amino acid derived from dietary methionine by demethylation. Homocysteine may be further metabolized by the transulfuration pathway to cysteine, of remethylated using either methyltetrahydrofolate or betaine. Vitamin B12 is a cofactor for methionine synthase, and vitamin B6 is a cofactor for cystathione β synthase and cystathionase. Increased concentrations of homocysteine may be caused by inherited enzyme defects or acquired deficiencies of vitamins B6,B12 or folate. Cystathione β synthase deficiency is the most common genetic cause of severe hyperhomocysteinemia. The homozygous trait is rare (occurring in 1 in 200,000 births) and is associated with plasma homocysteine concentrations of up to 400 μmol/L (30). Heterozygotes have an plasma homocysteine level of 20-40 μmol/L, about 2 to 4 times over normal (31). Heterozygous defects of some other genes could produce the same increase in plasma homocysteine levels (32-35).

Vitamin status and homocysteine

Homocysteine concentrations are increased in the presence of deficiency of B12, folate or B6. Suboptimal folate nutrition (less than 400 μg/day) is a common cause for mild hyperhomocysteinemia, and has been postulated as part of the link between of low intake of fruit and vegetables and premature cardiovascular disease (36).

Measurement of plasma homocysteine

Homocysteine is a sulfur-containing amine acid formed during metabolism of methionine. Homocysteine exist in normal human plasma in several different forms. Approximately 70% is bound to plasma proteins, mainly albumin. The remaining homocysteine combines with other thiols, including cysteine, resulting in mixed disulfide and homocysteine itself, to form the dimmer homocysteine. Only about 1% normally circulates as the free thiol compound. It is not known which form of homocysteine is directly involved in pathological processes. Hence measurement of homocysteine as a cardiovascular risk factor involves assay of total plasma homocysteine - that is combination of bound, free, reduced, and oxidized forms. The assays involve the conversion of all forms into a single species. Several techniques can be used for determination of homocysteine in plasma: radioenzymatic assays, ion exchange chromatography, high performance liquid chromatography (HPLC). Some of these methods are laborious, cumbersome, and expensive, require specific equipment and are unsuitable for routine work. A critical analysis of the methods used was published recently (36). The most suitable method for clinical purposes is HPLS with fluorescence detection (37).

Normal total plasma homocysteine concentration range from 5-15 μmol/L in the fasting state (38). Hyperhomocysteinemia could be divided into: moderate (16-30 μmol/L), intermediate (>30-100 μmol/L), and severe (>100 μmol/L) (3).

Investigation of moderate hyperhomocysteinemia

Subjects with total plasma homocysteine concentrations above 16 μmol/L require further investigation. The common cause is renal failure, however, hypothyroidism, pernicious anemia, cancer, drugs and toxins could be involved.

Individuals with creatinine concentrations in the range of 150-500 μmol/L typically have homocysteine values in the range of 20-30 μmol/L.

Folate and B12 status should also be assessed. Patients with frank vitamin deficiency will generally have homocysteine values greater than 20 μmol/L, but borderline vitamin levels alone give rise to borderline homocysteine levels.

Determination of methylene tetrahydrofolate reductase genotype could refine diagnosis. This can be determined by relatively simple techniques based on the polymerase chain reaction (39). Most persons who are homozygous for this mutation have "normal" homocysteine concentrations, but in the presence of suboptimal folate intake may develop hyperhomocysteinemia (15).

Deficiency of vitamin B6 is a rare cause of hyperhomocysteinemia and its measurement is not generally required for clinical purposes.

Treatment of moderate hyperhomocysteinemia

Specific disorders require specific treatments, i.e. parenteral B12 administration in pernicious anemia. For non-specific hyperhomocysteinemia, treatment with folic acid is usually the most effective. However, before folic acid is prescribed it is necessary to exclude vitamin B12 deficit, to prevent neurological damage with inappropriately prescribed folic acid rather than B12. The optimum dose of folic acid for the treatment of moderate hyperhomocysteinemia has not been determined yet. Standard treatments comprise 5 mg of folic acid daily. The major sources of folate in the diet are fruits and vegetables.

Addition of B6 supplements has been reported to have little additional homocysteine lowering effect but can be added in doses of 10-25 mg daily (40).

Hyperhomocysteinemia in renal failure is relatively resistant to treatment with vitamins, although some reduction could be achieved with folic acid (21).

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HIPERHOMOCISTEINEMIJA - FAKTOR RIZIKA ZA NASTANAK KARDIOVASKULARNOG OBOLJENJA

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Kratak sadržaj: *Kardiovaskularna i periferna vaskularna oboljenja su danas glavni uzrok morbiditeta i mortaliteta u opštoj populaciji. U poslednjih deset godina hiperhomocisteinemija je opisana kao nezavisan faktor rizika za aterosklerotično oboljenje krvnih sudova. Umerena hiperhomocisteinemija sreće se u 5-7% opšte populacije, a u trećoj i četvrtoj deceniji života povezana je sa prevremenom pojavom koronarne bolesti, šloga, arterijskih i venskih tromboza. Povišen nivo homocisteina može se sniziti primenom folne kiseline. Ovaj kratak pregled opisuje uticaj hiperhomocisteinemije na kardiovaskularni morbiditet, i daje aktuelan pristup prevenciji i lečenju.*

Ključne reči: *Hiperhomocisteinemija, koronarna bolest, šlog, venski tromboembolizam, faktor rizika*

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