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Hyperhomocysteinemia: a risk factor for arterial and venous thrombotic disease

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Abstract Patients with the rare homozygous hereditary defects of homocysteine metabolism that cause severe hyperhomocysteinemia and homocystinuria are at high risk of arterial and venous thrombosis. This prompted studies of the relationship between moderate hyperhomocysteinemia and thrombotic risk in the general population. In the last 2 decades, retrospective case-control studies and prospective cohort studies have demonstrated moderate hyperhomocysteinemia to be a frequent and independent risk factor for premature vascular disease in the coronary, cerebral, and peripheral arteries. More recently, the association of moderate hyperhomocysteinemia with venous thrombosis was shown in patients with early-onset or recurrent disease and in the general population. Genetic and environmental factors act in concert to cause moderate hyperhomocysteinemia. Since inadequate intake of folic acid, vitamin B₁₂, or vitamin B₆ are most frequently associated with hyperhomocysteinemia, dietary supplementation of these vitamins could have a tremendous impact on the epidemiology and natural history of arterial and venous thrombotic diseases.

Key words Homocysteine · Atherosclerosis · Thrombosis · Vitamins · Diet

Introduction

The incidence of arterial and venous thromboembolism, which is still the most common cause of morbidity and mortality in the Western World, can be decreased by the implementation of effective and safe treatment and prophylaxis strategies, and by the identification and subsequent modification of risk factors.

Among the identified risk factors, very few are common to both arterial and venous thrombosis. Hypercholesterolemia is a risk factor for coronary artery disease (CAD), but not for deep vein thrombosis and pulmonary embolism. In contrast, abnormalities of the natural anticoagulants protein C, protein S, and antithrombin are important risk factors for venous thromboembolism, whereas they are not clearly associated with an increased risk for arterial thrombosis [1].

In the last 2 decades, a growing amount of interest has focused on the role of moderate hyperhomocysteinemia in the pathogenesis of thromboembolic diseases. Two important features distinguish hyperhomocysteinemia from other known risk factors for thrombosis. It is associated with increased risk for both arterial and venous thrombosis. In addition, it can be easily corrected with safe and relatively inexpensive therapeutic approaches, such as dietary supplementation of folic acid and other vitamins, which could have a tremendous impact on the epidemiology and natural history of thrombotic diseases.

Homocysteine

Homocysteine is a sulphydryl amino acid derived from the metabolic conversion of methionine. Its intracellular metabolism occurs through enzymatic pathways that are dependent on vitamins as cofactors (Fig. 1). There are two pathways of remethylation of homocysteine to methionine. In that catalyzed by methionine synthase, the methyl group is donated by methyltetrahydrofolate and cobalamin acts as a cofactor. In the other pathway, betaine is the methyl donor and the reaction is catalyzed by betaine-homocysteine methyltransferase. In the transulfuration pathway, homocysteine is transformed by cystathionine-β-synthase (CBS) in cystathionine, with pyridoxal-5'-phosphate, a vitamin B₆ derivative, acting as a cofactor. Vitamin B₆ is also necessary for transformation of cystathionine to cysteine and α-ketobutyric acid.
Homocysteine is oxidized in plasma to the disulfides homocysteine-homocysteine (homocystine) and homocysteine-cysteine (mixed disulfide). Homocysteine and the two disulfides exist both in free and protein-bound forms and are globally referred to as total homocysteine (tHcy) or homocyst(e)ine, whose concentration in normal plasma ranges between 5 and 15 μmol/l. Only a small fraction of tHcy is present in plasma as non-protein-bound, reduced homocysteine.

Causes of hyperhomocysteinemia

The most frequent cause of severe hyperhomocysteinemia (characterized by basal levels of homocysteine higher than 100 μmol/l) is homozzygous deficiency of CBS, which has a prevalence in the general population of approximately 1:200 000–1:335 000 [2]. Affected individuals develop the classical syndrome of homocystinuria, characterized by mental retardation, ectopic lens, skeletal abnormalities, premature vascular disease, and thromboembolism. Approximately 5%–10% of cases of severe hyperhomocysteinemia are caused by inherited defects of remethylation. Homozygous deficiency of methylene-tetrahydrofolate reductase (MTHFR), which catalyzes the reduction of methylenetetrahydrofolate to methyltetrahydrofolate, is the most common inherited defect of the remethylation pathway and characterized by neurological dysfunction, psychomotor retardation, seizures, peripheral neuropathy, premature vascular disease, and thromboembolism.

Moderate forms of hyperhomocysteinemia (basal levels of tHcy between 15 and 100 μmol/l) are encountered in phenotypically normal subjects with genetic defects, acquired conditions, or, more frequently, a combination of both. Genetic defects associated with moderate hyperhomocysteinemia cause approximately a 50% reduction in activities of the corresponding enzymes, such as heterozygosity for CBS or MTHFR deficiency, whose cumulative prevalence in the general population is between 0.4% and 1.5% [3]. Another genetic defect that is associated with a 50% reduction of the enzymatic activity is characterized by the presence of a thermolabile mutant of MTHFR [4], which is due to the homozygous C to T substitution at nucleotide 677 of the encoding gene, converting the codon for alanine to that for valine [5]. The prevalence of homozygosity for the C677T mutation varies between 5% and 20% in subjects of Caucasian descent. Moderate elevations of plasma tHcy levels are not found in all subjects with genetic defects causing a 50% reduction of the corresponding enzyme activities, indicating that their phenotypic expression can be influenced by other factors. For instance, homozygotes for the thermolabile form of MTHFR have high homocysteine levels mainly in the presence of low serum concentrations of folic acid [6, 7]. Other determinants of plasma Hcy levels are gender, age, cigarette smoking, arterial hypertension, hypercholesterolemia, and lack of physical exercise [8].

Causes of acquired hyperhomocysteinemia include deficiencies of folate, cobalamine, and pyridoxine, which are essential cofactors for homocysteine metabolism, and chronic renal insufficiency. Vitamin deficiencies are the most frequent cause of hyperhomocysteinemia, especially in elderly people [9–11]. Drugs interfering with the metabolism of folate, such as methotrexate and anticonvulsants, of cobalamin, such as nitrous oxide, and of vitamin B6, such as theophylline, can cause moderate hyperhomocysteinemia [12, 13].

Diagnosis of hyperhomocysteinemia

The diagnosis of hyperhomocysteinemia is usually based upon the measurement of the plasma levels of tHcy by high-performance liquid chromatography with electrochemical or fluorescent detection. Measurement of plasma homocysteine 2–8 h after a standardized oral methionine load (3.8 g/m² body surface area or 0.1 g/kg body weight) allows improved distinction of normal individuals and subjects with mild abnormalities of homocysteine metabolism [2, 14]. Epidemiological studies have shown that both basal and post-methionine load levels or net increments above fasting levels of tHcy are associated with increased risk for thrombosis. The cutoff point for hyperhomocysteinemia is usually set at the 95th percentile of the homocysteine distribution in healthy subjects; since tHcy levels are affected by gender, different cutoff points should be used for men and women.

Hyperhomocysteinemia in arterial thrombosis

The hallmark of inherited homocystinuria, irrespective of the type of enzymatic defect that is responsible for the