Homocysteine, Vitamin B6 and the Risk of Recurrent Venous Thromboembolism

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Key words
Homocysteine · Venous thrombosis
Recurrence · Vitamin B6

Abstract
Hyperhomocysteinemia (HHC) is an independent risk factor for cardiovascular disease, and even mildly to moderately elevated homocysteine levels have been associated with a heightened risk for a first and recurrent venous thromboembolism (VTE). Within the frame of a large prospective cohort study (Austrian Study on Recurrent Venous Thromboembolism), we assessed the impact of HHC on the risk of recurrence among 602 patients with a first unprovoked VTE. HHC was an independent risk factor of recurrence conferring a relative risk of 1.5 (95th% CI 1.0-2.4). HHC is caused either by genetic defects and/or by a deficiency of the vitamins (B12, B6 and folic acid) involved in the homocysteine metabolism. Low vitamin B6 levels are associated with an increased risk of a first venous thrombosis. We currently investigate whether or not low plasma levels of PLP are associated with a heightened risk for recurrent VTE.

Hyperhomocysteinemia (HHC) is an independent risk factor for cardiovascular disease, and even mildly to moderately elevated homocysteine levels have been associated with a heightened risk for a first VTE [1]. HHC is caused either by genetic defects and/or by a deficiency of the vitamins (B12, B6 and folic acid) involved in the homocysteine metabolism [2]. The mechanisms by which HHC might contribute to atherogenesis and thrombogenesis are still incompletely understood.

VTE is a common disorder with an annual incidence of 1 to 2 % [3]. The most serious complication of VTE is recurrence which is fatal in approximately 5 to 10 % of patients [4]. The risk of recurrence is extremely high during the first few weeks after the acute event and then declines over time. To prevent recurrent VTE patients are given antithrombotic therapy which consists of heparin treatment followed by administration of oral anticoagulants. Anticoagulant treatment is very effective as recurrent VTE is rarely encountered during this period of time. These drugs, however, can cause severe or fatal bleeding. Thus, choosing the optimal duration of prophylaxis for an individual patient entails balancing the risk of hemorrhage against the risk of recurrent VTE. The risk for severe bleeding associated with oral anticoagulation has been repeatedly investigated and ranges between 1 and 2%/year [5-7]. There is, in contrast, only limited data on the risk of recurrent VTE. To pinpoint patients at high risk of recurrence by defining their individual risk...
Homocysteine is a sulfur amino acid whose metabolism stands at the intersection of two pathways: remethylation to methionine, which requires folate and vitamin B12 (or betaine in an alternative reaction); and transsulfuration to cystathionine, which requires pyridoxal-5'-phosphate, the coenzyme form of vitamin B6. Mild hyperhomocysteinemia seen in fasting conditions is due to mild impairment in the methylation pathway (i.e. folate or vitamin B12 deficiencies or methylenetetrahydrofolate reductase thermolability). Post-methionine-load HHC may be due to heterozygous cystathionine beta-synthase defect or vitamin B6 deficiency. In a case-control study, low plasma levels of pyridoxal-5' phosphate (PLP), the coenzyme form of vitamin B6, were associated with a heightened risk for a first VTE [9]. This association was independent of known risk factors for VTE, including high plasma levels of homocysteine, which is under the metabolic control of B vitamins, including vitamin B6. Within the frame of AUREC, we currently investigate whether or not low plasma levels of PLP are also associated with a heightened risk for recurrent VTE.

There are some indirect indications that the association of low PLP levels with arterial and venous thrombosis may be causal. In two observational studies vitamin B6 supplementation indeed affected the clinical outcome of the patients. Patients who were given vitamin B6 for carpal tunnel syndrome and other degenerative diseases were found to have 27% of the risk of developing acute cardiac chest pain or myocardial infarction, compared with patients who had not taken vitamin B6 [10]. The use of vitamin preparations containing vitamin B6 was associated with a lower incidence of atherothrombotic events in 8008 women [11]. In uncontrolled intervention studies the high risk of both arterial and venous thrombosis among patients with homocystinuria due to cystathionine-β-synthase deficiency was considerably reduced by the supplementation of high-dose vitamin B6 in combination with other vitamins. Importantly, the protective effect of vitamin B6 could be observed despite the lack of complete normalization of the plasma homocysteine levels [12]. Thus, it might be hypothesized that vitamin B6 exerts protective effects not only by decreasing homocysteine levels but by other (unknown) mechanisms.

Homocysteine exerts a protective effect not only by decreasing homocysteine levels but by other (unknown) mechanisms.
References