Homocysteine, Vitamin B6 and the Risk of Recurrent Venous Thromboembolism

Sabine Eichinger

Dept. of Internal Medicine I, Div. of Hematology and Hemostasis, Allgemeines Krankenhaus Wien, Austria

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.

Copyright © 2004 S. Karger AG, Basel

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

KARGER

Fax +41 61 306 12 34
E-Mail: karger@karger.ch
www.karger.com

© 2004 S. Karger AG, Basel
1424-8832/04/0336-0342\$21.00/0

Accessible online at:
www.karger.com/pht

Sabine Eichinger, MD
Dept. of Internal Medicine I
Div. of Hematology/Hemostasis
Allgemeines Krankenhaus Wien
A-1090 Wien, Austria

Tel: +43-1-40400-4410; E-mail: sabine.eichinger@meduniwien.ac.at

profile is one of the foremost goals in thrombosis research. The "Austrian Study on Recurrent Venous Thromboembolism" (AUREC) is the largest study worldwide to tackle this target. AUREC was initiated in 1992 and is an ongoing prospective multicenter cohort study currently including 2000 patients. Inclusion criteria for AUREC are an objectively documented episode of VTE, at least 3 months of anticoagulation and an age of at least 18 years. Exclusion criteria are antithrombin-, protein C- or protein S-deficiency, presence of the lupus anticoagulant, need for long-term antithrombotic treatment, history of cancer or active cancer, and pregnancy. The principal endpoint of the study is recurrence of symptomatic VTE confirmed by venography, perfusion/ventilation lung scan or spiral computed tomography.

Within the frame of AUREC we demonstrated that patients with HHC are at a high risk of recurrent VTE [8]. This study, however, had some limitations: 1) the number of patients (264) as well as the observation time (mean 23 months) were limited, 2) at the time of publication the impact of high factor VIII on the risk of recurrence was unknown and, thus, data were not adjusted for high factor VIII, and 3) patients were classified as having HHC if their homocysteine levels exceeded the 95th percentile of healthy control subjects rather than selecting the threshold among the thrombosis patients. To overcome these limitations we reassessed the impact of homocysteine on the risk of recurrent VTE among 602 patients with a first unprovoked VTE who were prospectively followed for a mean of 49 ± 34 months. Homocysteine levels were determined in venous blood collected after overnight fasting which was immediately centrifuged, snap-frozen and stored at -80°C . The total homocysteine concentration was measured in the citrated plasma by high performance liquid chromatography under isocratic conditions at room temperature using an acetate-buffer with fluorometric detection.

One-hundred of 602 patients (17%) had recurrent VTE. We stratified patients into two groups according to their homocysteine levels ($\geq$ and $<$ 75th percentile of thrombosis patients). Since homocysteine levels are higher among men than among women, the 75th percentile was $10.9\text{ }\mu\text{mol/L}$ for men and $9.5\text{ }\mu\text{mol/L}$ for women. Two years after discontinuation of oral anticoagulants, the probability of recurrent VTE was 17.7% (95th% CI 11.1-24.2%) in patients with HHC (75th percentile of thrombosis patients) as compared with 7.6% (95th% CI 5.1- 10.1%) in patients without HHC. Patients with high HHC had a 1.6-fold increased relative risk (RR) of recurrence (95th% CI 1.0-2.4) as compared with those without HHC. The increased RR of recurrence remained almost unchanged after adjustment for age, sex, factor V Leiden, prothrombin G20210A and high FVIII (RR 1.5; 95th% CI 1.0-2.4).

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 its protective effects not only by decreasing homocysteine levels but by other (unknown) mechanisms.

References

- 1 Cattaneo M: Hyperhomocysteinemia and thrombosis. *Lipids*. 2001;36 Suppl:S13-26. Review.
- 2 Selhub J. Homocysteine metabolism. *Annu Rev Nutr*. 1999;19:217-46.
- 3 Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, Forcier A, Dalen JE: A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med* 151:933-938.
- 4 Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS: Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *JAMA* 1998;279:458-462.
- 5 Palareti G, Leali N, Coccheri S, Poggi M, Manotti C, D'Angelo A, Pengo V, Erba N, Moia M, Ciavarella N, Devoto G, Berrettini M, Musolesi S: Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. *Lancet* 1996;348:423-428.
- 6 van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briet E: Assessment of a bleeding risk index in two cohorts of patients treated with oral anticoagulants. *Thromb Haemost* 1996;76:12-16.
- 7 Levine MN, Raskob G, Landefeld S, Kearon C: Hemorrhagic complications of anticoagulant treatment. *Chest* 1998;114:511S-513S.
- 8 Eichinger S, Stümpflen A, Hirschl M, Bialonczyk C, Herkner K, Stain M, Schneider B, Pabinger I, Lechner K, Kyrle PA: Hyperhomocysteinemia is a risk factor of recurrent venous thromboembolism. *Thromb Haemost* 1998;80:566-569.
- 9 Cattaneo M, Lombardi R, Lecchi A, Bucciarelli P, Mannucci PM: Low plasma levels of vitamin B(6) are independently associated with a heightened risk of deep-vein thrombosis. *Circulation* 2001;104:2442-2446.
- 10 Ellis JM, McCully KS: Prevention of myocardial infarction by vitamin B6. *Res Commun Mol Pathol Pharmacol* 1995;89:208-220.
- 11 Rimm EB, Willett WC, Hu FB, Sampson L, Colditz GA, Manson JE, Hennekens C, Stampfer MJ: Folate and vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women. *JAMA* 1998;279:359-364.
- 12 Wilcken DE, Wilcken B: The natural history of vascular disease in homocystinuria and the effects of treatment. *J Inher Metab Dis*. 1997;20:295-300.