Hyperhomocysteinemia and venous thrombosis : studies into risk and therapy

Willems, H.P.J.

Chapter 7

Hyperhomocysteinemia as a risk factor for venous thrombosis in elderly patients

HPJ Willems, M den Heijer, M Havekes, SVloet, WBJ Gerrits,
HWA Berenschot, HJ Blom, GMJ Bos, FR Rosendaal

Submitted for publication

Abstract

High plasma levels of homocysteine are a risk factor for venous thrombosis. Although thrombosis has a high incidence in elderly people, little is known about the risk of venous thrombosis related to hyperhomocysteinemia in the elderly .

We performed a case-control study with 426 patients with a first, idiopathic and objectively diagnosed deep-vein thrombosis or pulmonary embolism and 294 control subjects from the general population. All subjects were >65 years of age.

Mean homocysteine levels were higher in the cases (14.4 (95% CI 13.9 to 14.9) µmol/l) than in the controls (13.2 (95% CI 12.7 to 13.7) µmol/l). There was a linear relationship between quartiles of homocysteine concentration and thrombosis risk, with an odds ratio for the highest versus the lowest quartile of 1.7 (95% CI 1.1 to 2.7).

We conclude that mild hyperhomocysteinemia is a risk factor for venous thrombosis in the elderly.

Introduction

Venous thrombosis is a common disease, especially in the elderly. The incidence rises from approximately 25 / 100,000 / year at the age of 25 to 500 / 100,000 / year over the age of 80[1]. Immobility, malignancy and major surgery are well known environmental risk factors for venous thrombosis. These may in part explain why elderly patients are more at risk for developing venous thrombosis since the prevalence of these risk factors is higher at higher age, but it cannot explain the steep rise in incidence that is seen in the elderly.
High levels of homocysteine are an established risk factor for venous thrombosis. The association has been established in numerous case-control studies and three prospective studies[2]. Most of these studies did not focus on elderly patients. Since plasma homocysteine levels increase exponentially with age[3], homocysteine might play an important role in the development of venous thrombosis in this age group. Two previous studies have reported on the risk of hyperhomocysteinemia and the development of venous thrombosis and the relation with age. Den Heijer *et al*. found a sharp increase in the risk of thrombosis with age associated with hyperhomocysteinemia for both men and women[4]. The results of this study could not be confirmed by Tsai *et al*. who found no association between hyperhomocysteinemia and an increased risk of thrombosis at high age[5]. More studies on this subject are lacking. We therefore performed a case-control study among elderly patients to evaluate whether elevated homocysteine levels are a risk factor for venous thrombosis in this age group.

Patients and methods

Cases

Cases were selected from the screening of the VITRO (vitamin and thrombosis) study. The design of the study was described previously[6]. In short, the VITRO study is a randomized, placebo-controlled, double-blind trial with multivitamin B as secondary prevention of venous thrombosis in patients with hyperhomocysteinemia. Patients for the trial were selected from seven anticoagulation clinics in the Netherlands from February 1995 to June 2000. Anticoagulation clinics monitor the treatment of virtually all patients on coumarins in a well described geographic area. All patients who were registered for treatment for a first deep-vein thrombosis or pulmonary embolism

were eligible for screening and asked to donate an extra blood tube for homocysteine measurement.
In the current analysis we included patients from the anticoagulation clinics of The Hague and Rotterdam who were aged 65 years or older at the time of a first event of idiopathic venous thrombosis, which was diagnosed by objective methods (proximal deep-vein thrombosis by compression-ultrasonography or phlebography, pulmonary embolism by high-probability VQ-scanning, pulmonary angiography or spiral CT scanning). We considered as idiopathic events that were not preceeded by immobilisation (bed-rest, paresis, cask), major trauma or major surgery, vasculitis or intravenous catheters, or malignancy). Information on diagnostic methods and these risk factors were obtained from the treating physician.

Control subjects

Control subjects were selected from two general practices in The Hague and Rotterdam. In the Hague all persons of 65 years and older registered at this practice were asked by mail to participate. In the Rotterdam practice we randomly invited 500 persons of 65 years and older from all patients registered at the practice. They were eligible for participation in the absence of a previous venous thrombosis and malignancy. People with a malignancy were excluded from the analysis.

Blood handling

Blood was drawn before 10 a.m. in acidic citrate tubes (Biopool Stabilyte^{TM}). In a previous study we showed that acidic citrate stabilizes whole blood for measurement of homocysteine at 21°C[7,8]. Blood was stored at room temperature and was processed within 5 hours after collection. It was centrifuged for 10' at 2000*g* in a non-cooled centrifuge. The plasma was separated and stored at -30°C until determination of the homocysteine concentration.
Homocysteine was determined by automated high-performance liquid chromatography (HPLC) with reverse phase separation and fluorescent detection (Gilson 232-401 sample processor (Gilson Medical Electronics Inc., Middleton,WI), Spectra-Physics 8800 solvent delivery system and Spectra-Physics LC 304 fluorometer (San Jose,CA)), according to the method described by Fiskerstrand *et al.*[9] with some modifications[10,11]. Homocysteine concentrations were multiplied by 10/9 as correction for the fluid present in the blood tube prior to collection.

Data analysis

We calculated age and sex specific quartiles of homocysteine. The odds ratios for the second to the fourth quartile (with the first quartile as a reference category) was calculated with a logistic regression model.

Results

At the anticoagulation clinics of The Hague and Rotterdam we screened 2821 patients for the VITRO study. Of these, 1195 were above 65 years. We obtained information about circumstances and diagnostic methods of the venous thrombosis of 1097 patients. Of these, 110 patients had a recurrence, and 572 patients had a first, idiopathic venous thrombosis of which 146 were not objectively diagnosed according to our entry criteria. This left 426 patients who met the participation criteria for the current study.
From 1045 persons invited by mail to participate as control subject, 294 consented to participate. Baseline characteristics of the patients and controls are shown in Table 7.1. There were more men in the patient group than in the control group (46% vs. 41%) and the mean age was higher in the patients group (74.5 vs 73.2 years).

Table 7.1 Baseline characteristics of the patients and controls.

	patients	controls
number	426	294
men / women	196 / 230	120 / 174
median age (range) in years	74 (65-93)	72 (65-96)
mean homocysteine (range) in µmol/l	13.2 (12.7-13.7)	14.4 (13.9 – 14.9)
thrombosis		
deep-vein thrombisis	255	
pulmonary embolism	135	
both	36	

The distribution of the homocysteine concentrations of patients and control subjects is shown in Figure 7.1. Homocysteine was higher in men (1.5 (95% CI 0.7 to 2.4) µmol/l) and increase with age both in men (3.0 (95% CI 0.8 to 5.2) per decade) and women (2.2 (95% CI 1.3 to 3.2) per decade). Therefore, we calculated the odds ratios for thrombosis for age- and sex- specific quartiles with the lowest quartile as the reference quartile (Figure 7.2). We found a linear dose-response relationship with an odds ratio for the highest versus the lowest

quartile of 1.7 (95% CI 1.1 to 2.7). There was no apparent difference in risk in the different age and sex groups. Stratification for type of thrombotic event did not show clear differences in risk for deep-vein thrombosis (odds ratio top versus bottom 1.9 (1.2 to 3.0)), pulmonary embolism (1.5 (0.8 to 2.7) or both (1.4 (95% CI 0.5 to 3.8).

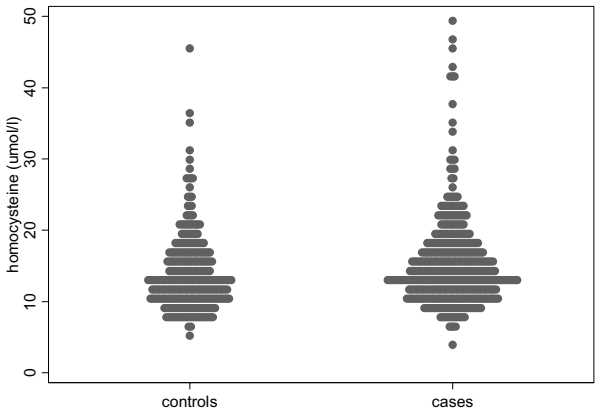

Figure 7.1 Distribution of homocysteine concentrations of controls and cases (in µmol/l).

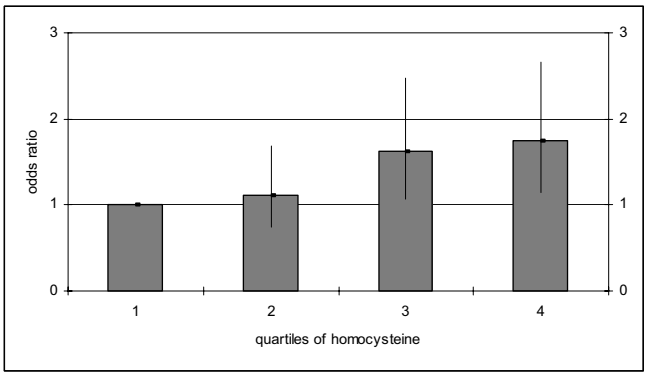

Figure 7.2 Thrombosis risk for age- and sex specific quartiles of homocysteine concentrations.

Discussion

We found that the homocysteine concentration in plasma is a risk factor for venous thrombosis in elderly individuals as it is among younger people.

Furthermore, we found a graded increase in the risk with increasing homocysteine concentrations.

The risk estimate that we report in this study lies between that of our earlier study[4] and the study of Tsai and colleagues[5]. In a case control study with 269 patients with a deep-vein thrombosis and 269 age- and sex- matched controls we reported an increase in relative risk for hyperhomocysteinemia from 0.7 (95% CI 0.1 to 4.0) under the age of 30, up to 5.5 (95% CI 1.2 to 5.2) over the age of 50. This graded increase in risk was seen in both men and women.

However, Tsai and colleagues looked at homocysteine as risk factor for venous thromboembolism in the LITE study, a nested case-control study[5]. They found an overall odds ratio of 1.55 (95% CI 0.93 to 2.58) for the highest versus the lowest quintile. They report an attenuation of the association with increasing age, and absence of any excess risk above 65 years.

In the current study the risk estimate, as an odds ratio, is very similar to those reported in studies in younger patient groups. Even though the odds ratios we calculated are similar to those in studies of younger subjects, this may imply that the absolute effect of hyperhomocysteinemia is greater among the elderly, because the incidence of thrombosis is much higher[1].

In conclusion, homocysteine is a risk factor for venous thrombosis in patients above 65 years old.

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