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Hyperhomocysteinemia and Venous Thrombosis: A Meta-analysis

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Summary

Hyperhomocysteinemia is an established risk factor for atherosclerosis and vascular disease. Until the early nineties the relationship with venous thrombosis was controversial. At this moment ten case-control studies on venous thrombosis are published. We performed a meta-analysis of these reports.

We performed a MEDLINE-search from 1984 through June 1997 on the keywords "homocysteine" or "hyperhomocysteinemia" and "venous thrombosis", which yielded ten eligible case-control studies.

We found a pooled estimate of the odds ratio of 2.5 (95% CI 1.8-3.5) for a fasting plasma homocysteine concentration above the 95th percentile or mean plus two standard deviations calculated from the distribution of the respective control groups. For the post-methionine increase in homocysteine concentration we found a pooled estimate of 2.6 (95% CI 1.6-4.4).

These data from case-control studies support hyperhomocysteinemia as a risk factor for venous thrombosis. Further research should focus on the pathophysiology of this relationship and on the clinical effects of reducing homocysteine levels by vitamin supplementation.

Introduction

Homocysteine is an amino acid, which was discovered in 1932 by Vigneaud as a product of transmethylation of methionine, an essential amino acid (1). In the early sixties Carlson et al. as well as Gerritsen et al. found very high levels of the disulphate homocystine in the urine (homocystinuria) of some infants with mental retardation (2-4). In 1964 Mudd and colleagues reported the absence of cystathionine-β-synthase activity in the liver of a subject with homocystinuria (5). Because homocystinuria was found to be associated with vascular disease at young age, it was supposed, that also the carrier state for homocystinuria might be a risk factor for vascular disease. This carrier state was thought to be identical with mildly elevated homocysteine levels, particularly after methionine loading. Up to now, more than thirty case-control studies have been published which show an increased risk for vascular disease due to hyperhomocysteinemia (6).

Although Mudd reported as early as 1985 that 51% of the vascular events in severe homocystinuria were of venous origin (7), the first studies on the relation between mild hyperhomocysteinemia and venous thrombosis were not published until 1991 (8, 9). From 1991 to now in total eight case-control studies are published, which are subject of the present review.

Methods

We performed a MEDLINE-search from 1984 through June 1998 on the keywords "homocysteine" or "hyperhomocysteinemia" and "venous thrombosis". We found a total of 117 articles of which 12 contain data from case-control studies on venous thrombosis (8-19). Two papers reported the same study (8, 10). One study concerned only women using oral contraceptives and reported only mean homocysteine concentrations (11). Therefore this study was not included in the meta-analysis. Also the follow-up study of Kyrle et al. was left out because this study concerned the risk of recurrent venous thrombosis after a first event (20).

We derived the numbers of cases and control subjects with and without hyperhomocysteinemia from the ten remaining studies. Hyperhomocysteinemia was defined according to the reported study as a plasma homocysteine concentration above the 95th percentile or mean plus 2 (or 2.7) times the standard deviation calculated from the distribution of the respective control groups (for the study of Simioni only data about the 90th percentile were available). Because most studies with the methionine loading test used post-methionine increase in homocysteine concentration rather than absolute values we reanalysed one study on recurrent venous thrombosis in terms of homocysteine increase (13). We calculated (unmatched) odds ratios for each of the studies with corresponding confidence intervals, using Woolf's method.

A pooled estimate was calculated by a Mantel-Haenszel method. This method was used because two studies had no subjects with hyperhomocysteinemia in their control group. So, for these studies no individual odds ratio could be calculated. The confidence intervals of the Mantel-Haenszel estimates were calculated by using the method of Robins (21). We also tested for homogeneity as reported by Greenland (22). This test could only be applied to those studies for which odds ratios can be calculated. Therefore we left out two studies with no control subjects with hyperhomocysteinemia.

Results

Ten studies examined the relationship between hyperhomocysteinemia and venous thrombosis (Table 1). The odds ratios for the fasting state as well as after methionine loading are shown in Fig. 1.

In 1991 Bienvenu et al. (8, 10) found elevated homocysteine levels in a group of 17 patients with venous thrombosis compared to 49 control subjects. The same study was published in English language in 1993 with 23 patients and 49 control subjects. The patient group included patients with rare presentations of venous thrombosis as Budd-

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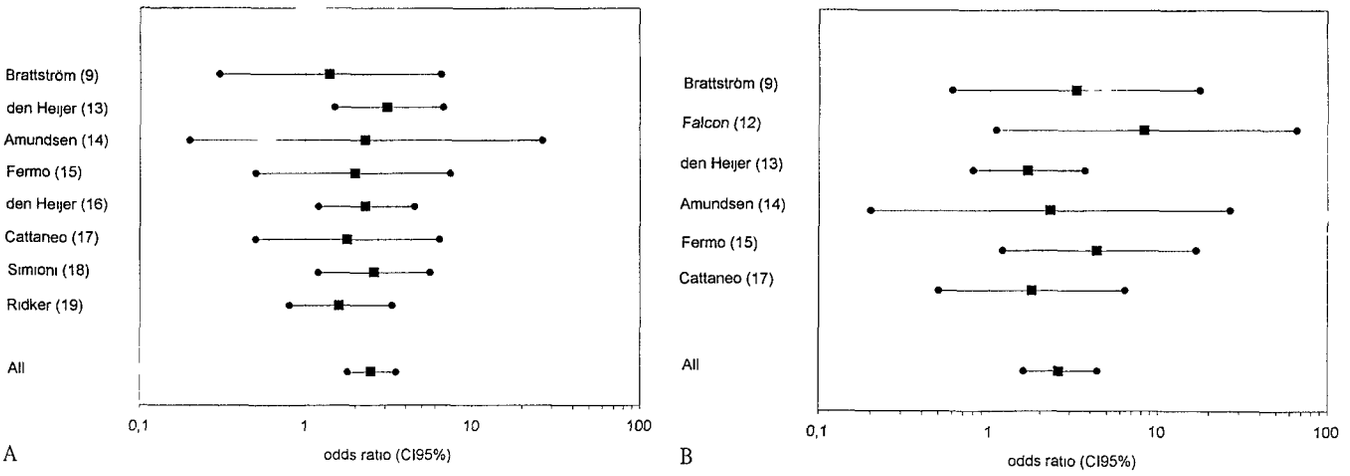

Fig. 1A, B The odds ratios according to elevated fasting homocysteine levels (A) or elevated post-methionine homocysteine increase (B) in case-control studies on venous thrombosis. Two studies (10, 12) are left out in the figure on fasting homocysteine levels because no odds ratios could be calculated

Chiari syndrome, central retinal vein occlusion and mesenterical venous thrombosis.

Brattström et al. (9) reported no significant difference in mean plasma homocysteine between patients with venous thrombosis and controls in a small series of 42 patients and 42 controls. Interestingly, from their data on post-methionine increase a 3-fold elevated risk of hyperhomocysteinemia for thrombosis could be calculated, which remained non-significant likely due to the small sample size.

In 1994 Falcon et al. reported hyperhomocysteinemia as a risk factor for thrombosis occurring before the age of forty (12). They studied patients with one or more episodes of venous thrombosis including cerebral vein thrombosis (and excluding other thrombophilic disorders), and healthy control subjects from the hospital staff. They reported a difference in homocysteine level between cases and controls particularly after methionine loading. In 1995 we found hyperhomocysteinemia to be a risk factor for recurrent venous thrombosis in patients between 20 and 70 years of age when compared to controls from the general population (13).

Other studies, published in 1995 are the study of Amundsen et al., who found no significant difference in mean homocysteine in 35 patients (age less than 56) with deep-vein thrombosis and 39 controls (14) and the study of Fermo et al. who found significantly higher prevalence of hyperhomocysteinemia in 107 patients with venous thrombosis before the age of 45 compared with 60 healthy persons (15). They also found an increased recurrence rate in patients with hyperhomocysteinemia.

In 1996, we reported a population-based case-control study in patients with a first, objectively confirmed, episode of deep-vein thrombosis and control subjects of the general population (16). Another population-based study was published by Cattaneo et al. who studied 89 patients with a first episode of deep-vein thrombosis and 89 age and sex matched controls (17). Both studies found an increased risk for venous thrombosis due to hyperhomocysteinemia.

Simioni et al. published a study in 60 patients with proven DVT and as control subjects patients who were referred to the hospital because of clinically suspected DVT but had normal venograms; they found an odds

Table 1 Characteristics of ten studies on hyperhomocysteinemia and venous thombosis

First author	Kind of throm-bosis (age)	Number of thrombotic episodes	Cut-off point	Fasting (F) / Post-load (P)	Cases with HH/ total cases	Controls with HH/ total controls
Bienvenu[8,10]	VT (<60)	?	mean +2 7 SD	F	7/23	0/49
Brattström[9]	DVT/PE (<50)	1	mean + 2 SD	F	4/42	3/42
				P	6/42	2/43
Falcon[12]	VT (<50)	1	mean + 2 SD	F	7/80	0/51
				P	14/79	1/40
den Heijer[13]	DVT/PE (20-90)	2	95th perc[$]	F	24/185	10/220
				P	15/185	11/220
Amundsen[14]	DVT (<56)	1	mean + 2 SD	F	2/35	1/39
				P	2/35	1/39
Fermo[15]	VT (<45)	1	95th perc	F	10/107	3/60
				P	11/58	3/60
den Heijer[16]	DVT (16-70)	1	95th perc	F¶	28/269	13/269
Cattaneo[17]	DVT	1	95th perc	F	7/89	4/89
				P	7/89	4/89
Simioni[18]	DVT	1	90th perc	F	15/60	17/148
Ridker[19]	DVT	1	95th perc	?	10/145	29/646

[$] derived from original data
HH= hyperhomocysteinemia
DVT= deep-vein thrombosis
¶ in this study non-fasting samples were used
VT= all kinds of venous thrombosis
PE= pulmonary embolism

ratio of 2.6 (18). Ridker et al. investigated homocysteine levels in the Physicians' Health Study in 145 men who subsequently developed venous thromboembolism and 646 men free of cardiovascular disease (19). They concluded that hyperhomocysteinemia was associated with idiopathic venous thrombosis but not with venous thrombosis of any cause.

So, eight studies found hyperhomocysteinemia to be a risk factor for venous thrombosis and two studies reported no relationship between hyperhomocysteinemia and venous thrombosis. The other Fig. 1 shows that all studies from which an odds ratio could be calculated, have point estimates of the odds ratio above 1.4. The pooled estimate for the fasting homocysteine levels of all eight studies is 2.5 (95%CI 1.8-3.5). For the post-methionine increase in homocysteine concentration we found a pooled estimate of 2.6 (95% CI 1.6-4.4). The test for homogeneity – which was restricted to those studies for which odds ratios could be calculated – did not reach significance for either the fasting homocysteine level ($\chi^2 = 2.23$, $p > 0.9$, $df = 7$) as well as for the post-load homocysteine increase ($\chi^2 = 3.36$, $p > 0.5$, $df = 5$); the distribution of the effect measures over the studies, as shown in Figs. 1A and 1B, also does not point to heterogeneity of effect.

Discussion

The pooled estimates for fasting homocysteine and post-methionine increase confirm the conclusion of most – except of two (9, 14) – studies that hyperhomocysteinemia is a risk factor for venous thrombosis. Notably, the odds ratios calculated for these two studies are very similar to the pooled estimate. The negative conclusions of these two studies are based on comparing mean homocysteine levels in patients and control subjects and not on odds ratios as estimates of risk.

Two studies are yet published which provide prospective data. The study of Ridker et al. showed that subjects with increased homocysteine levels are at increased risk for future venous thromboembolism (19). Kyrle et al. reported that patients who already suffered from deep-vein thrombosis had a higher risk for recurrences if they had elevated homocysteine levels (20). These two studies strengthen the hypothesis that homocysteine is causally associated with venous thrombosis.

The pooled estimates for both the fasting homocysteine level and the post-methionine homocysteine increase are very similar. It is believed that fasting homocysteine levels are more associated with remethylation defects while post-load increase of homocysteine are more associated with transsulfuration defects. The similarity in odds ratios does not point out whether venous thrombosis is more associated with remethylation defects or transsulfuration defects. The question whether patients with venous thrombosis should underwent a methionine loading test or that measurement of fasting homocysteine would be enough could not be answered on the base of this meta-analysis because we have no information about the correlation between fasting homocysteine concentrations and post-load homocysteine increase.

Despite this epidemiological evidence for the relationship between hyperhomocysteinemia and venous thrombosis, little is known about its pathophysiology. A magnitude of possible mechanisms is proposed with respect to vascular disease, which have been reviewed by several authors (23-25). Many of these proposed mechanisms with respect to arterial vascular disease may be applied to venous thrombosis as well. However, most hypotheses are based on in vitro experiments using very high and unphysiological concentrations of homocysteine.

The clinical relevance of the finding that hyperhomocysteinemia is a risk factor for venous thrombosis depends mainly on its treatability by vitamin supplementation. Especially folic acid has a strong homocysteine lowering effect (26-27). However, no data on clinical intervention studies are yet available and it cannot be ruled out that homocysteine is an epiphenomen with respect to thrombosis, in which case vitamin supplementation would probably be ineffective (28).

In conclusion, there is increasing evidence that mild hyperhomocysteinemia is a risk factor for venous thrombosis. Further research should focus on the pathophysiology of thrombosis in hyperhomocysteinemia and on the clinical effects of homocysteine lowering by means of vitamin supplementation as well as on the interaction of this very common abnormality with other genetic or acquired thrombogenic defects.

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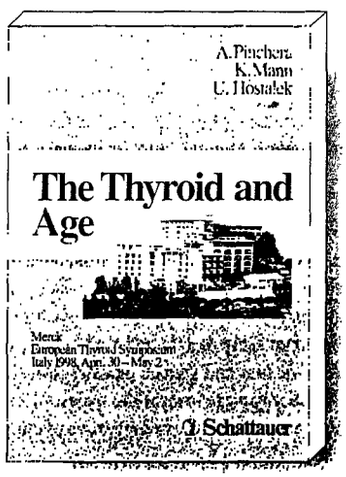

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Prevalence, clinical manifestations and therapeutic requirements of thyroid disorders greatly differ during the course of life. There is a variety of diagnostic and therapeutic problems in pregnant women which are relevant not only for the endocrinologist, but also for the pediatrician and the gynecologist. The development of the fetal thyroid and the pathogenesis of genetic diseases are only partly understood. Screening for thyroid diseases in the newborn and early treatment are often inconsequentially performed.

In puberty, early diagnosis and prevention of thyroid diseases are of tremendous socio-economical relevance, as most goiters develop at this age. In adults, iodine deficiency remains a world-wide risk that is responsible for morbidity resulting from nodular goiter and thyroid autonomy. Iodine excess is a common cause of iatrogenic thyroid disorders.

Thyroid diseases in the elderly are often unrecognized and may substantially contribute to morbidity and mortality.

It is the aim of this book to focus the attention on age dependent aspects of thyroid diseases and their specific diagnosis and treatment.

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