A Cross-Sectional Study to Detect the Prevalence of Hyperhomocysteinemia in Cases of Deep Vein Thrombosis

Gautam V. Kamat · S. C. Metgud ·
Vishwanath M. Pattanshetti · A. S. Godhi

Received: 27 August 2009 / Accepted: 3 October 2009 / Published online: 19 November 2010
© Association of Surgeons of India 2010

Abstract Hyperhomocysteinemia is a known risk factor for the development of deep vein thrombosis (DVT). Various studies have been conducted in the western countries to know the prevalence of hyperhomocysteinemia in patients with DVT and in general population. There is no documented literature of the prevalence of hyperhomocysteinemia in Indian population. Thus the aim of this study was to determine the prevalence of hyperhomocysteinemia in cases of DVT in our population. To evaluate the prevalence of hyperhomocysteinemia, a prospective cross sectional study done on a total of 70 patients admitted in KLES Dr Prabhakar Kore hospital, Belgaum, India. DVT was confirmed by Doppler examination. Serum homocysteine was measured and the data analysed. Statistical significance was calculated using chi square test. A total of 70 patients were studied of which 53 were males and 17 were females. The prevalence of hyperhomocysteinemia among the cases of DVT was 31.428%. The prevalence among males was 35.85% and among females was 17.64%. There was statistically significant association between hyperhomocysteinemia and presence of ischaemic heart disease with a *p* value of 0.005 on chi square analysis. The prevalence of hyperhomocysteinemia in cases of deep vein thrombosis in our population was 31.428%. There was a statistically significant association between hyperhomocysteinemia and ischaemic heart disease.

Keywords Hyperhomocysteinemia · Deep vein thrombosis

Introduction

Deep vein thrombosis is a common but elusive illness that can result in suffering and death if not recognized and treated early. Since venous thrombosis is difficult to recognize clinically, these hospitalized cases probably represent the tip of the iceberg.

An association between the risk of venous thromboembolism and a hypercoagulable state has been recognized for many years. Mild hyperhomocysteinemia is an established risk factor for atherosclerosis and vascular disease [1, 2]. In classic homocysteinuria, half the vascular complications are of venous origin [3]. Various studies have proven that hyperhomocysteinemia is a risk factor for venous thrombosis [4, 5]. Prevalence of hyperhomocysteinemia in cases of deep vein thrombosis has been extensively studied in the western population, but there are very few studies showing its prevalence in Indian population.

Thus, the present study was undertaken with the aim to determine the prevalence of hyperhomocysteinemia in cases of Deep Vein Thrombosis in KLES Dr Prabhakar Kore hospital, Belgaum.

Metabolism of Homocysteine (Fig. 1)

Homocysteine is a sulphur-containing amino acid that is mainly derived from dietary methionine. Under normal metabolic circumstances, about 50% of the homocysteine formed is remethylated to methionine. This remethylation requires two key enzymes: methionine synthase (MS) and methylenetetrahydrofolate reductase (MTHFR). The MS

G. V. Kamat · S. C. Metgud · V. M. Pattanshetti (✉) · A. S. Godhi
JN Medical College,
Belgaum, India
e-mail: drvmshetti@gmail.com

Fig. 1 Metabolism of Homocysteine

uses vitamin B₁₂ as a cofactor and 5-methyltetrahydrofolate as a methyl donor. When there is an excess of protein or methionine, a larger proportion of homocysteine is metabolized by irreversible transsulfuration pathway, which degrades homocysteine to cysteine. In this, homocysteine is first sulfconjugated to cystathionine by cystathionine beta-synthase (CBS). Cystathionine is further cleaved into cysteine by cystathionine γ -lyase. Both enzymes need vitamin B₆ as a cofactor.

from the institutional ethical committee. The participants were included in the study after obtaining their written informed consent. Details of the patient like name, age, sex, inpatient number, history of smoking, diabetes mellitus (DM), ischaemic heart disease (IHD), hypertension (HTN) were recorded in the proforma.

Inclusion criteria All patients with deep vein thrombosis confirmed by Doppler ultrasound were included in the study. There were no exclusion criteria.

Patients and Methods

This study was conducted in KLE'S Dr Prabhakar Kore hospital and Medical Research Centre, Belgaum from December 2006 to December 2007. Approval was obtained

Method of Homocysteine Estimation

2 cc of over night fasting venous blood sample was collected in EDTA bulb from the cubital vein and sent for serum homocysteine estimation to the biochemistry laboratory.

Fig. 2 Age distribution

Fig. 3 Sex-wise distribution

Fig. 4 Risk factor analysis

The ELISA method was used for the estimation of serum homocysteine levels. *Hyperhomocysteinemia* (Hyper-Hcy) was defined as a serum homocysteine level of more than 16.0 in male patients and a serum homocysteine level of more than 20.4 in female patients.

Statistical Analysis

The prevalence was calculated using the following formula:

$$\text{Prevalence} = \frac{\text{Number of patients with DVT with hyperhomocysteinemia}}{\text{Total number of patients with DVT}} \times 100$$

Statistical analysis for significance of difference between age, sex, and presence or absence of the risk factors such as DM, HTN, smoking, IHD, immobilization and trauma and surgery, was done using Chi-Square test with Yate's correction.

Observations and Results

A total of 70 patients satisfied the selection criteria. Out of these 70 patients, 22 patients were found to have raised

serum homocysteine levels. The prevalence of hyperhomocysteinemia in this study was calculated as 31.428%.

On analysis with Chi-square test the *P* value for the difference in age distribution (Fig. 2) in the two groups was 0.6519 showing its insignificance. The prevalence of hyperhomocysteinemia among males was 35.85% and that among females was 17.64% (Fig. 3). The *P* value for the sex distribution difference in the two groups was 0.268 showing that the difference was insignificant. The *P* value for the distribution of risk factors (Fig. 4, Table 1) in the two groups was significant in patients with IHD wherein the *P* value was 0.005. In case of all the other risk factors the *P* value was >0.05 showing that the difference was insignificant.

Discussion

Hyperhomocysteinemia is a proven risk factor for deep vein thrombosis. Elevated homocysteine concentrations have been found in 40% of patients with vascular disease and 35% of patients with venous thromboembolism [5]. A study by Den Heijer M showed a prevalence of hyperhomocysteinemia as 10% [6]. Simioni et al. in their case control study showed that the prevalence of hyperhomocysteinemia was 25% [7]. In our study the prevalence of hyperhomocysteinemia in patients with DVT was found to be 31.428%. Thus our study shows that the prevalence of hyperhomocysteinemia in patients with DVT is higher in our Indian population as compared to western population.

Falcon et al. found that hyperhomocysteinemia was a risk factor for thrombosis in people younger than 40 years of age [4]. Hyperhomocysteinemia is a risk factor for recurrent venous thrombosis in patients between 20 and 70 years of age, as compared with controls from the general population [6]. In our study there was no statistical

Table 1 Risk Factors

Risk factors	Total % (n=70)	Hyper-Hcy %	
		(n=22)	<i>p</i> value
Trauma/surgery	15.71	9.01	<i>p</i> =0.498
Immobilization	5.71	13.64	<i>p</i> =0.168
Smoking	46.75	59.1	<i>p</i> =0.385
HT	37.14	54.55	<i>p</i> =0.061
DM	41.43	54.55	<i>p</i> =0.131
IHD	11.43	31.81	<i>p</i> =0.005

significance in the prevalence of hyperhomocysteinemia among the different age groups.

In our study the sex wise prevalence of hyperhomocysteinemia was 35.85% in males as compared to 17.64% in females. Thus the prevalence was higher in males as compared to females. This is consistent with finding in other studies [5, 6, 8].

In the distribution of risk factors in the two groups IHD was significant with a *P* value was 0.005. Hyperhomocysteinemia is also associated with arterial thrombosis [6, 9, 10] and is an established risk factor for atherosclerosis and vascular disease [1, 2, 9–11]. The association between mild hyperhomocysteinemia and venous thrombosis is similar in degree to that reported for hyperhomocysteinemia and arterial vascular disease [12, 13]. Thus in our study, there is a statistically significant association between hyperhomocysteinemia and IHD.

Although smoking is a known risk factor for hyperhomocysteinemia, this study did not show any statistically significant association between them.

Conclusion

The prevalence of hyperhomocysteinemia in cases of deep vein thrombosis in our population was 31.428%. There was a statistically significant association between hyperhomocysteinemia and ischaemic heart disease. Smoking was not a statistically significant risk factor for hyperhomocysteinemia.

Blood concentrations of homocysteine are inversely related to blood concentrations of folate, vitamin B-12, and, to a lesser extent, vitamin B-6 [14]. Dietary supplements of these vitamins are used to reduce homocysteine concentrations in subjects who have high blood concentrations of homocysteine.³

In subjects with hyperhomocysteinemia a reduction of plasma fasting homocysteine concentration by folic acid and vitamins B₁₂ and B₆ administration is associated with reduction of thrombin generation both in peripheral blood and at sites of haemostatic plug formation [15]. Low dose folic acid, pyridoxine and cobalamin are effective inexpen-

sive low risk pharmacological options to lower and maintain the homocysteine concentration in population at risk. We recommend measurement of homocysteine levels in all cases of deep vein thrombosis and starting the patient on long term or life long folic acid and vitamin B₁₂ therapy in patients with hyperhomocysteinemia.

References

1. Undas A, Brozek J, Szczeklik A (2005) Homocysteine and thrombosis: from basic science to clinical evidence. *Thromb Haemost* 94:907–15
2. Rees MM, Rodgers GM (1993) Homocysteinemia: association of a metabolic disorder with vascular disease and thrombosis. *Thromb Res* 71:337–359
3. Mudd SH, Skovby F, Levy HL (1985) The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet* 37:1–31
4. Falcon CR, Cattaneo M, Panzeri D et al (1994) High prevalence of hyperhomocysteinemia in patients with juvenile venous thrombosis. *Arterioscler Thromb* 14:1080–1083
5. Den Heijer M, Blom HJ, Gerrits WBJ (1995) Is hyperhomocysteinemia a risk factor for recurrent venous thrombosis? *Lancet* 345:882–885
6. Den Heijer M, Koster T, Blom HJ (1996) Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. *N Engl J Med* 334:759–762
7. Simioni P, Pradoni P, Burlina A et al (1996) Hyperhomocysteinemia and deep- vein thrombosis. A case-control study. *Thromb Haemost* 76(6):883–6
8. Rosen P, Barkin RM (1998) *Emergency Medicine: Principles and Practice*. Vol 3. 4th ed. St. Louis, Mosby; Chapter 107;1123–1154
9. Malinow MR (1990) Hyperhomocyst(e)inemia: a common and easily reversible risk factor for occlusive atherosclerosis. *Circulation* 81:2004–2006
10. Frohlich JJ (1995) Lipoproteins and homocyst(e)ine as risk factors for atherosclerosis: assessment and treatment. *Can J Cardiol* 11:18C–23C
11. Fortin LJ, Genest J Jr (1995) Measurement of homocyst(e)ine in the prediction of arteriosclerosis. *Clin Biochem* 28:155–162
12. Selhub J, Jacques PF, Bostom AG (1995) Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. *N Engl J Med* 332:286–291
13. Stampfer MJ, Malinow MR, Willett WC (1992) A prospective study of plasma homocysteine and risk of myocardial infarction in US physicians. *JAMA* 268:877–881
14. Selhub J, Jacques PF, Wilson PW et al (1993) Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *JAMA* 270:2693–8
15. Undas A, Domagala TB, Jankowski M et al (1999) Treatment of hyperhomocysteinemia with folic acid and vitamins B12 and B6 attenuates thrombin generation. *Thromb Res* 95(6):281–8