

# PREVALENCE OF HYPERHOMOCYSTEINEMIA IN PATIENTS WITH RETINAL VEIN OCCLUSION

M. R. Manaviat\*, M. R. Shoja and M. R. Besharaty

Department of Ophthalmology, School of Medicine, Yazd University of Medical Sciences, Yazd, Iran

**Abstract-** Recently multiple studies have shown that elevated homocysteine levels may be associated with ophthalmic vascular disease. To investigate the role of high plasma levels of homocysteine in the patients with retinal vein occlusion, 21 patients with retinal vein occlusion (RVO) and 20 age and sex matched controls without RVO were included in this retrospective case-control study. Information regarding sex, age, blood pressure, history of diabetes, history of glaucoma were obtained from all participants. Plasma level of homocysteine was measured by high plasma liquid chromatography. Mean plasma total homocysteine level was significantly higher in patients than controls ( $14.17 \pm 9.91$  versus  $8.97 \pm 3.10$   $\mu\text{mol/L}$ ,  $P < 0.031$ ). Hyperhomocysteinemia was present in 5 of the 21 patients (25%) but only one control had elevated plasma homocysteine (5%). Hyperhomocysteinemia is highly associated with retinal vein occlusion; therefore, its measurement may be useful in the management of these patients.

*Acta Medica Iranica*, 44 (6): 420-424; 2006

© 2006 Tehran University of Medical Sciences. All rights reserved.

**Key words:** Retinal vein occlusion, hyperhomocysteinemia, folic Acid

## INTRODUCTION

Hyperhomocysteinemia is accepted nowadays as an independent risk factor for cardiovascular disease, atherosclerosis and peripheral vascular disease (1-2). The homocysteine theory of atherosclerosis was proposed 35 years ago by McCully (3). Increased homocysteine levels may also be a risk factor for the development of stroke, osteoporosis, inflammatory bowel disease and miscarriage (1).

Homocysteine (2 amino – 4-mercapto – butanoic acid) is a non – protein forming amino acid produced by the metabolism of methionine. Methionine regenerates by retrieving the methyl radical through the action of methylene tetrahydrofolate reductase (MTHFR). This process is called remethylation.

Alternatively, homocysteine can follow the transulfuration route where it is irreversibly converted into cysteine or glutathione. Hyperhomocysteinemia results from enzyme deficiency in the process of remethylation or transulfuration (Cystathionine  $\beta$ - Synthase “CBS”).

There are other conditions that may increase plasma homocysteine levels: age, male gender, renal failure, white race, postmenopause, diabetes mellitus, medications, caffeine, alcohol, tobacco and decrease in uptake of vitamins B6, B12 and folic acid (4). Recently multiple studies have shown that elevated homocysteine levels may be associated with ophthalmic vascular disease. (4-10) On the other hand, hyperhomocysteinemia can be effectively treated with folic acid. Therefore, prospective trials are underway to determine the role of homocysteine and folate therapy in the pathogenesis and treatment of these conditions. The aim of our study was to examine the prevalence of hyperhomocysteinemia among patients with retinal vein occlusion and the results were compared with age matched control group obtained by the same laboratory.

Received: 17 Oct. 2005, Revised: 2 Apr. 2005, Accepted: 18 May 2005

### \* Corresponding Author:

M. R. Manaviat, Department of Ophthalmology, School of Medicine, Yazd University of Medical Sciences, Yazd, Iran

Tel: +98 351 8224100

Fax: +98 21 8224100

E-mail: mr\_manaviat@yahoo.com

## MATERIALS AND METHODS

In this retrospective study, all patients with retinal vein occlusion were evaluated, including branch retinal vein occlusion, central retinal vein occlusion or hemiretinal vein occlusion. Our control group consisted of consecutive patients of similar gender and age without any history of retinal disease.

This study was done at department of ophthalmology, Yazd University of medical sciences between March 2004 and April 2005.

Any patient with a history of renal failure or taking medications that elevate the serum homocysteine was excluded. Demographic data and blood pressure were recorded. Fasting blood sugar (after 8-10 hours of fasting), cholesterol and triglycerides (after 12 hours of fasting) were measured by autoanalyzer. Ophthalmic data including intraocular pressure, visual acuity, neovascular complications, type of vascular involvement and ischemic or non-ischemic type also were recorded. Fasting venous blood was obtained from each participant for the laboratory evaluation, blood samples was centrifuged within the first hour of collection to remove plasma from blood cells.

Samples were analyzed by high-performance liquid chromatography (HPLC). The reference range for normal in our laboratory was 15  $\mu\text{mol/L}$  or less after overnight fasting. The study was approved by the institutional review board.

Data were analyzed using SPSS 11.5 for windows. The Chi square test and ANOVA were used for comparing groups and data were presented as means  $\pm$  standard deviations. A *P* value of 0.05 or less was considered statistically significant.

## RESULTS

Twenty one patients with retinal vein occlusion including 12 patients with central retinal vein occlusion (CRVO), 6 patients with branch retinal vein occlusion (BRVO) and 3 hemi-retinal vein occlusion cases were compared with 20 control subjects. The mean age of the cases ( $52.47 \pm 12.73$  years) was not significantly different (*P* = 0.91) from the controls ( $52.05 \pm 11.02$  years).

**Table 1.** Characteristics of cases with retinal vein occlusion and control subjects

| Characteristic                           | Cases             | Controls          |
|--|-------------------|-------------------|
| Number                                   | 21                | 20                |
| Mean age (years)                         | $52.47 \pm 12.73$ | $52.05 \pm 11.02$ |
| Sex (Male/Female)                        | 14/7              | 12/8              |
| Total homocysteine ( $\mu\text{mol/L}$ ) | $14.17 \pm 9.91$  | $8.97 \pm 3.10$   |

There were similar proportions of men to women in the patients and controls (*P* = 0.65). Six patients had an ischemic central retinal vein occlusion. One of the 10 patients with CRVO had bilateral involvement.

The mean total plasma homocysteine level was  $14.17 \pm 9.91$   $\mu\text{mol/L}$  (range, 6-50.2) for patients and  $8.97 \pm 3.1$   $\mu\text{mol/L}$  (5-16.5) for controls (*P* = 0.031).

Five of the patients had a homocysteine level of more than 15  $\mu\text{mol/L}$  whereas only one of the controls was above this level. Summary of above mentioned values are shown in table 1.

## DISCUSSION

The results of our study demonstrate that a statistically significant association exists between elevated levels of homocysteine and retinal vein occlusion. In our study, of the 21 patients, five (25%) had elevated levels of homocysteine. In Vine study this was 21.6% (4). According to Lahey and colleagues (8) 9.5% of patients with CRVO were found to have hyperhomocysteinemia. In a meta-analysis by Cahill and co-workers a total of 614 patients with any type of vein occlusion were compared with 762 control subjects in nine studies (4). Mean total homocysteine levels in cases were between 10.2 and 18.4 but in controls this figures were between 7 and 14 ( $\mu\text{mol/L}$ ). The trend was for higher total homocysteine levels in cases when compared with controls and the combined standard difference was significant (4). Our study had similar results for cases (14.1) and for controls (8.97).

Retinal vein occlusive disease can involved central trunks or branches of the retinal veins and is a significant cause of ocular morbidity. Although retinal vein occlusion has a number of common known risk factors including hypertension, diabetes and arteriosclerosis, but young otherwise healthy

## Hyperhomocysteinemia and retinal vein occlusion

adults with retinal vein occlusion raise questions as to the etiology of vein occlusion and the classic risk factors do not fully explain these relationships. Recently, elevated plasma homocysteine has been shown to be an independent risk factor for retinal vein occlusion in some studies (11-21).

However, not all reported studies have demonstrated a relationship between elevated plasma homocysteine and retinal vein occlusion (22-24). These later studies support the hypothesis that hyperhomocysteinemia is more likely a marker of atherosclerosis and the consequence of other well established risk factors.

Similarly, elevated plasma homocysteine has been shown to be an independent risk factor for central retinal artery occlusion (CRAO) (4, 5, 14, 15, 20), ischemic optic neuropathy (5), Behçet's disease (25) and pseudoexfoliation glaucoma (26).

The etiology of elevated serum homocysteine is multifactorial. Homocysteine is a metabolite of methionine and can be converted back to methionine or to cysteine via remethylation or transsulfuration. The enzyme methylenetetrahydrofolate reductase (MTHFR) is a pivotal enzyme in homocysteine metabolism. The genetically determined thermolabile variant of MTHFR which exerts less enzymatic activity has received considerable attention. However, most reported studies fail to demonstrate correlation between homozygosity for thermolabile MTHFR and retinal vascular disease (4, 21, 23, 27, 28). These contrasting reports of the relation between TT genotype and total homocysteine (tH) levels may be related to the age of the patients studied. Genetic determinants of tH may be more important in younger patients with premature vascular disease, whereas nutritional factors may be more important in older patients (28).

The most important nutritional factors include the vitamins folate, B6 and B12 and excessive intake of methionine rich proteins (7). Therapy with folic acid, vitamin B6 and Vitamin B12 has been shown to lower homocysteine levels and may prevent venous occlusive disease in patients with hyperhomocysteinemia (8). Increasing age, male gender, race, renal failure, diabetes mellitus, hypothyroidism and psoriasis, tobacco smoking and excessive alcohol and caffeine also are known factors that elevate tH levels (4). The increasing level of homocysteine in patients with retinal vein occlusion probably reflects numerous

causes, including lifestyle determinants, serum vitamin status and genetic components. The exact mechanism by which homocysteine affects the vascular system is poorly understood, but there is increasing evidence that homocysteine decreases production of prostacyclin, nitric oxide and thrombomodulin production (7). In addition, endothelial cell damage occurs by the generation of reactive oxygen species such as superoxide anions and hydrogen peroxide (4). There is also experimental evidence that homocysteine can accelerate the development of atherosclerotic lesions by initiating a cascade of inflammatory pathways mediated by tissue factor and receptor for advanced glycation end products (4).

Our study has the following limitations: it was retrospective; homocysteine was not measured at the time of the acute retinal vein occlusion. It is possible that the homocysteine levels may have changed after the initial diagnosis of retinal vein occlusion. Treatment of associated systemic diseases such as hypertension would result in decreased plasma homocysteine levels (6). Recently it has been shown that homocysteine levels elevated after tissue infarction (4). Therefore higher homocysteine levels after ischemic events may be a result rather than a cause of the acute vascular event. Another source of confusion regarding homocysteine is the multiple methods of laboratory measurements leading to different normal ranges. Our study demonstrates that elevated plasma homocysteine is statistically more prevalent in patients with retinal vein occlusion. Although large – scale randomized prospective trials will be required to confirm that reducing plasma homocysteine levels results in decreased atherothrombotic vascular disease.

Treatment of hyperhomocysteinemia is relatively simple, safe and inexpensive and numerous studies have proposed that a dietary folic acid supplement should be recommended to reduce plasma homocysteine levels in the general population (6). In conclusion, we currently recommend that the assessment of patients with retinal vein occlusion should include measurement of total plasma homocysteine especially in young patients and those without common main risk factors.

## Conflict of interests

We have no conflict of interests.

## REFERENCES

1. Aguilar B, Rojas JC, Collados MT. Metabolism of homocysteine and its relationship with cardiovascular disease. *J Thromb Thrombolysis*. 2004 Oct; 18(2):75-87.
2. Nygard O, Nordrehaug JE, Refsum H, Ueland PM, Farstad M, Vollset SE. Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med*. 1997 Jul 24; 337(4):230-236.
3. McCully KS. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. *Am J Pathol*. 1969 Jul; 56(1):111-128.
4. Cahill MT, Stinnett SS, Fekrat S. Meta-analysis of plasma homocysteine, serum folate, serum vitamin B(12), and thermolabile MTHFR genotype as risk factors for retinal vascular occlusive disease. *Am J Ophthalmol*. 2003 Dec; 136(6):1136-1150.
5. Pianka P, Almog Y, Man O, Goldstein M, Sela BA, Loewenstein A. Hyperhomocystinemia in patients with nonarteritic anterior ischemic optic neuropathy, central retinal artery occlusion, and central retinal vein occlusion. *Ophthalmology*. 2000 Aug; 107(8):1588-1592.
6. Vine AK. Hyperhomocysteinemia: a risk factor for central retinal vein occlusion. *Am J Ophthalmol*. 2000 May; 129(5):640-644.
7. Brown BA, Marx JL, Ward TP, Hollifield RD, Dick JS, Brozetti JJ, Howard RS, Thach AB. Homocysteine: a risk factor for retinal venous occlusive disease. *Ophthalmology*. 2002 Feb; 109(2):287-290.
8. Lahey JM, Tunc M, Kearney J, Modlinski B, Koo H, Johnson RN, Tanaka S. Laboratory evaluation of hypercoagulable states in patients with central retinal vein occlusion who are less than 56 years of age. *Ophthalmology*. 2002 Jan; 109(1):126-131.
9. Van Cott EM, Laposata M, Hartnett ME. Prothrombin gene mutation G20210A, homocysteine, antiphospholipid antibodies and other hypercoagulable states in ocular thrombosis. *Blood Coagul Fibrinolysis*. 2004 Jul; 15(5):393-397.
10. Lahey JM, Kearney JJ, Tunc M. Hypercoagulable states and central retinal vein occlusion. *Curr Opin Pulm Med*. 2003 Sep; 9(5):385-392.
11. Marcucci R, Bertini L, Giusti B, Brunelli T, Fedi S, Cellai AP, Poli D, Pepe G, Abbate R, Prisco D. Thrombophilic risk factors in patients with central retinal vein occlusion. *Thromb Haemost*. 2001 Sep; 86(3):772-776.
12. Martin SC, Rauz S, Marr JE, Martin N, Jones AF, Dodson PM. Plasma total homocysteine and retinal vascular disease. *Eye*. 2000 Aug; 14 ( Pt 4):590-593.
13. Hansen L, Kristensen HL, Bek T, Ingerslev J. Markers of thrombophilia in retinal vein thrombosis. *Acta Ophthalmol Scand*. 2000 Oct; 78(5):523-526.
14. Cahill M, Karabatzaki M, Meleady R, Refsum H, Ueland P, Shields D, Mooney D, Graham I. Raised plasma homocysteine as a risk factor for retinal vascular occlusive disease. *Br J Ophthalmol*. 2000 Feb; 84(2):154-157.
15. Wenzler EM, Rademakers AJ, Boers GH, Cruysberg JR, Webers CA, Deutman AF. Hyperhomocysteinemia in retinal artery and retinal vein occlusion. *Am J Ophthalmol*. 1993 Feb 15; 115(2):162-167.
16. Chua B, Kifley A, Wong TY, Mitchell P. Homocysteine and retinal vein occlusion: a population-based study. *Am J Ophthalmol*. 2005 Jan; 139(1):181-182.
17. Yildirim C, Yaylali V, Tatlipinar S, Kaptanoglu B, Akpinar S. Hyperhomocysteinemia: a risk factor for retinal vein occlusion. *Ophthalmologica*. 2004 Mar-Apr; 218(2):102-106.
18. Cabezas-Leon MM, Garcia-Montero MR, Morente-Matas P. [Hyperhomocysteinemia as a risk factor for central retinal vein thrombosis in a young patient]. *Rev Neurol*. 2003 Sep 1-15; 37(5):441-443. Spanish.
19. Blondel J, Glacet-Bernard A, Bayani N, Blacher J, Lelong F, Nordmann JP, Coscas G, Soubrane G. [Retinal vein occlusion and hyperhomocysteinemia]. *J Fr Ophtalmol*. 2003 Mar; 26(3):249-253. French.
20. Abu El-Asrar AM, Abdel Gader AG, Al-Amro SA, Al-Attas OS. Hyperhomocysteinemia and retinal vascular occlusive disease. *Eur J Ophthalmol*. 2002 Nov-Dec; 12(6):495-500.
21. Weger M, Stanger O, Deutschmann H, Temmel W, Renner W, Schmut O, Quehenberger F, Semmelrock J, Haas A. Hyperhomocyst(e)inemia, but not methylenetetrahydrofolate reductase C677T mutation, as a risk factor in branch retinal vein occlusion. *Ophthalmology*. 2002 Jun; 109(6):1105-1109.
22. Di Crecchio L, Parodi MB, Sanguinetti G, Iacono P, Ravalico G. Hyperhomocysteinemia and the methylenetetrahydrofolate reductase 677C-T mutation in patients under 50 years of age affected by central retinal vein occlusion. *Ophthalmology*. 2004 May; 111(5):940-945.

## Hyperhomocysteinemia and retinal vein occlusion

23. Boyd S, Owens D, Gin T, Bunce K, Sherafat H, Perry D, Hykin PG. Plasma homocysteine, methylene tetrahydrofolate reductase C677T and factor II G20210A polymorphisms, factor VIII, and VWF in central retinal vein occlusion. *Br J Ophthalmol*. 2001 Nov; 85(11):1313-1315.
24. Larsson J, Hultberg B, Hillarp A. Hyperhomocysteinemia and the MTHFR C677T mutation in central retinal vein occlusion. *Acta Ophthalmol Scand*. 2000 Jun; 78(3):340-343.
25. Okka M, Ozturk M, Kockar MC, Bavbek N, Rasier Y, Gunduz K. Plasma homocysteine level and uveitis in Behcet's disease. *Isr Med Assoc J*. 2002 Nov; 4(11 Suppl):931-934.
26. Leibovitch I, Kurtz S, Shemesh G, Goldstein M, Sela BA, Lazar M, Loewenstein A. Hyperhomocysteinemia in pseudoexfoliation glaucoma. *J Glaucoma*. 2003 Feb; 12(1):36-39.
27. Cruciani F, Moramarco A, Curto T, Labate A, Recupero V, Conti L, Gandolfo GM, Balacco Gabrieli C. MTHFR C677T mutation, factor II G20210A mutation and factor V Leiden as risks factor for youth retinal vein occlusion. *Clin Ter*. 2003 Sep-Oct; 154(5):299-303.
28. Cahill M, Karabatzaki M, Donoghue C, Meleady R, Mynett-Johnson LA, Mooney D, Graham IM, Whitehead AS, Shields DC. Thermolabile MTHFR genotype and retinal vascular occlusive disease. *Br J Ophthalmol*. 2001 Jan; 85(1):88-90.