Hyperhomocysteinemia and Central Retinal Vein Occlusion in Iranian Population

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Abstract

***Purpose*:** To evaluate total plasma homocysteine level during the acute phase of central retinal vein occlusion (CRVO) compared with a matched healthy group in Iranian population, and determine whether hyperhomocysteinemia is also a risk factor for CRVO.

***Methods*:** A study group contains 54 patients presenting with CRVO in recent one month, acute phase of the decease, was compared for fasting total plasma homocysteine level with a matched control group of 51 patients evaluated in the same clinic for a non retinal disease diagnosis.

***Results*:** The mean total plasma homocysteine level was 14.76±7.67 µmol/l in cases, and 11.42±3.74 µmol/l in control subjects. It shows a significant difference (p=0.005) in mean plasma homocysteine level between the cases and control group. Odds ratio of CRVO for individuals with hyperhomocysteinemia was 2.88 (95% CI=1.08-7.71 and p=0.03). The overall multivariable-adjusted odds of CRVO in participants with plasma homocysteine level above 15 µmol/l was 4.71 (95% CI=1.46-15.19 and p=0.009) Hyperhomocysteinemia was not statistically different in each age group (<60 years: 27%, 61-70 years: 33.3 %, 71-80 years: 31.6%, >81 years: 33.3%, Chi-square test, p=0.98)

***Conclusion*:** Elevated total plasma homocysteine level is an independent risk factor for CRVO in Iranian population. In addition to an evaluation of all conventional cardiovascular risk factors, measurement of total homocysteine for evidence of hyperhomocysteinemia may be important in the initial investigation and management of patients with CRVO.

***Keywords*:** central retinal vein occlusion, homocysteine, hyperhomocysteinemia, high-performance liquid chromatography

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Introduction

Homocysteine, is an intermediary metabolite of the essential dietary amino-acid methionine, metabolized by remethylation to methionine or by trans-sulfuration to cysteine. In the remethylation pathway, homocysteine is methylated to methionine by the enzyme methionine synthase. The methyl group is acquired from 5-methyl tetrahydrofolate and Cobalamin (vitamin B12) is essential for this reaction.[1,2]

Mean plasma homocysteine level shows a great inter-country variation ranging from 6 µmol/l, in Japan to 13 µmol/l, in South Africa.[3] Hyperhomocysteinemia refers to mild to moderate elevation of the amino acid homocysteine in blood or plasma. It may be caused by genetic determinants,[4] lifestyle determinants[5] (diet, coffee consumption), medications[6] (methotrexate), and clinical conditions[7] such as inadequate plasma concentrations of folate or B vitamins which are account for nearly two thirds of all cases of hyperhomocysteinemia in adults.[8]

It is now well documented that elevation of total plasma homocysteine level in a fasting state is associated with an increased risk of cardiovascular diseases such as myocardial infarction,[9,10] stroke,[11,12] and carotid intimal-medial wall thickening.[13] Extensive research in the recent decade has shown that hyperhomocysteinemia is an independent risk factor for vascular disease similar to smoking or hyperlipidemia.[14,15]

Recently hyperhomocysteinemia has also been implicated as an important modifiable potentially risk factor for retinal vein occlusions, especially central retinal vein occlusion (CRVO), which is among the most important causes of vision loss.[14-22] However data from some recent studies do not confirm this association[23-28] and it has not been reported in Iranian population yet. In a typical daily Iranian diet, the consumption of fresh fruits, vegetables, fresh herbs, tea, bread and rice is comparatively higher than a typical diet in Western Europe and the US. In a recent study, lower homocysteine levels observed in our population as compared to other populations.[29] The mean plasma homocysteine level in CRVO may also be subsequently lower in our population.

Thus we conducted a study to evaluate total plasma homocysteine level during acute phase of CRVO compared with a matched healthy group in Iranian population, to determine whether hyperhomocysteinemia is a risk factor for CRVO.

Methods

We conducted a case-control study on 105 individuals chosen among patients referred to Farabi Eye Hospital over a period of two years (March 2003 to February 2005). The study was reviewed and approved by the ethics committee of the Medical Faculty of Tehran University of medical sciences. Participants had no history of major systemic illness, evidence of vasculitits, renal, hepatic or thyroid disease, cardiomyopathy, pregnancy, and chronic alcohol abuse.

The study group contains 54 patients presenting with CRVO in recent one month, acute phase of the disease. CRVO was considered to be present if there was intra retinal hemorrhage in all four retinal quadrants surrounding the optic disk and scattered up to the periphery with venous dilation and tortousity. Control subjects were adult patients who evaluated in the same clinic for a nonretinal disease diagnosis like cataract and nasolacrimal duct obstruction. Controls were matched the study group patients in potential confounding factors such as age, sex, systemic hypertension, diabetes mellitus, and smoking states. A written informed consent was taken before blood sampling for measurmrnt of total plasma homocysteine level in this group.

The patients received complete ophthalmic and medical examinations, as well as laboratory evaluation including clotting tests. Fasting total plasma homocysteine level was measured in all patients by high-performance liquid chromatography. Hyperhomocysteinemia was defined as a total plasma homocysteine level above 15 µmol/l.

Descriptive statistics was used to report demographic characteristics; by the means of SPSS statistic package version 13.5. Independent sample t-test and chi-square test were also used to investigate the significance of quantitative and qualitative difference between homocystein levels in two groups. Logistic regression was used to analyze associations between total plasma homocysteine and CRVO. The adjusted odds

ratio was calculated as an estimate of the relative risk of CRVO for individuals with hyperhomocysteinemia. Multivariable-adjusted analyses controlled for statistically significant confounding variables of age, sex, hypertension, smoking history and serum creatinine, cholesterol, and triglyceride.

Results

Fifty four patients (22 females, 32 males) with CRVO were enrolled in the study. Control group included 51 individuals (22 females, 29 males). Analyses were performed on 105 participants with complete information on CRVO status and total plasma homocysteine level. Age and sex were not significantly different in two groups. Potential confounding risk factors such as diabetes mellitus, hypertension, smoking, and serum creatinine, cholesterol, and triglyceride levels were also compared between two groups. Patient's characteristics are shown in the table1.

The mean total plasma homocysteine level was 14.76±7.67 μmol/l in cases, and 11.42±3.74 μmol/l in control subjects. It showed a significant difference (p=0.005) in mean plasma homocysteine level between the cases and control group. 17 of 54 patients (31.5%) who were presented with CRVO, had total plasma homocysteine above 15 μmol/l, but only 7 of 51 (13.7%) control subjects. This difference was statistically significant (p=0.03)

Total homocysteine level above 15 μmol/l was nearly 2.5 times more common in patients with CRVO compared with healthy controls. In univariate analyses, odds ratio (OR) of CRVO for individuals with hyperhomocysteinemia was 2.88; (95% CI=1.08-7.71 and p=0.03).

Adjusted odds ratios of different variables are shown in table 2. The overall multivariable-adjusted odds of CRVO in participants with plasma homocysteine level above 15 μmol/l was 4.71; (95% CI=1.46-15.19 and p=0.009). Each 1 μmol/l increase in homocysteine level was associated with significant increased odds for CRVO 0.87; (95%CI=0.79-0.97, p=0.01). Hyperhomocysteinemia was not statistically different in each age group (<60 years: 27%, 61-70 years: 33.3%, 71-80 years: 31.6%,.> 81 years: 33.3%, Chi-square test, p=0.98).

Table 1. Descriptive data of CRVO and control subjects

	CRVO Group	Controls	p value
Number	54	51	
Age (year)	59.8±12.7 (22-87)	63.0±8.7 (41-78)	0.13
Male sex (%)	32 (59.3)	29 (56.9)	0.80
Hypertension (%)	16 (29.4)	16 (31.4)	0.84
Diabetes (%)	7.0	5.1	0.75
Hematocrit (%)	43.1±4.2 (30-52)	43.8±3.5 (34-69)	0.36
Creatinine (mg/dl)	0.98±0.17 (0.7-1.5)	1.00±0.23 (0.7-1.8)	0.70
Triglyceride (mg/dl)	189.6±73.4 (57-462)	194.2±69.9 (111-400)	0.76
Cholesterol (mg/dl)	201.7±42.2 (115-309)	185.9±41.6 (123-173)	0.07
Smoking (%)	9 (16.7)	5 (9.8)	0.30
Homocysteine level (μmol/L)	14.76±7.6 (5-38)	11.40±3.70 (6.2-23.9)	0.005
Homocysteine level >15 μmol/L (%)	17 (31.5)	7 (13.5)	0.03

Table 2. Adjusted Odds ratio of different risk factors in patient with CRVO

	Adjusted Odds ratio	Confidence interval	p value
Hypertension	1.72	0.54-5.41	0.35
Diabetes	1.55	0.16-14.67	0.70
Hematocrit	1.11	0.97-1.27	0.36
Creatinine	1.27	0.94-17.24	0.85
Triglyceride	1.00	0.99-1.01	0.51
Cholesterol	0.99	0.98-1.30	0.38
Smoking	1.18	0.21-6.52	0.84
Homocysteine level >15 µmol/L	4.71	1.46-15.19	0.009

Discussion

The result of this study demonstrated a clinically important and statistically significant association between the presence of hyperhomocysteinemia and CRVO. Compared with the control group, mean plasma total homocysteine levels were significantly higher in patients with retinal vascular occlusive disease (11.42 µmol/l versus 14.76 µmol/l). This is the first study to document that elevated plasma homocysteine level is an independent risk factor for CRVO in Iranian population.

Numerous studies have documented that hyperhomocysteinemia is a risk factor for cardiovascular disease.[9-13] Elevated total homocysteine is both an independent risk factor for atherosclerotic vascular disease[14,15] and interacts with other risk factors such as smoking and hypertension to increase cardiovascular disease risk.[30] The exact mechanism by which high plasma concentrations of homocysteine induce arterial and venous thrombosis is still not clear. There is evidence that homocysteine causes endothelial injury and dysfunction by increasing the production of free radicals generated from the oxidation of homocysteine and subsequent peroxidation. Homocysteine also stimulates the proliferation of vascular smooth muscle cells and inhibits the growth of vascular endothelial cells. This combination could lead to atherosclerosis. Other possible mechanisms of thrombosis in hyperhomocysteinemia include increased platelet adhesiveness, activation of the coagulation cascade, and impaired nitric oxide production from endothelial cells.[1,2] Because the central retinal vein shares a common, fibrous adventitia with the central retinal artery, it is likely that both arterial and venous diseases could contribute to the development of a CRVO. Any sclerotic thickening of the central retinal artery could easily compress the adjacent central retinal vein and begin the sequence of events that leads to thrombus formation.[31]

The results of the present study are in line with previous recent studies that have recognized hyperhomocysteinemia as a risk factor for retinal vascular occlusive disease especially CRVO.[14-22] However, most of these studies were retrospective,[14,21,22] subjects were not fasting at the time of homocysteine measurement,[14] cases and controls were not fully matched,[14,22] and homocysteine was not measured at the time of the acute retinal vascular occlusion.[14] This possible bias would result in lower values for the patients with CRVO. Further studies, including two very recent; found no correlation between CRVO and homocysteine.[23-28] One recent study suggests that the homocysteine plasma level is not a primary and independent risk factor for CRVO, but is more likely a marker of

atherosclerosis and the consequence of other well-established risk factors.[32]

Our study adds further support for a cardiovascular risk profile for persons with CRVO in Iranian population. These results also support the necessity of screening for possible hyperhomocysteinemia. in all patients with CRVO

Differing mean plasma homocysteine values for healthy people from various countries have been reported that range from 6 μmol/L in Japan to 13 μmol/L in South Africa.[3] In 1997, Alfthan et al [3] reported the mean plasma homocysteine concentrations in 13 different countries which ranged from 7.1 μmol/L in Germany to 10.7 μmol/L in Finland. The reason for inter-country variations of plasma homocysteine is not clear but Alfthan et al [3], argued that these differences are real and not due to non-compatible sampling and assay procedures. A lower homocysteine level reported in our country[29] is comparable with values obtained in France, Spain and Japan.[3] Geographical variation in fruit and vegetable intakes and particularly in dietary folate, might explain these inter-country differences. It has been suggested that a high dietary intake of folate can make a substantial contribution to the reduction in total plasma homocysteine concentrations in the general population.[29] In a typical daily Iranian diet the consumption of fresh fruits, vegetables, fresh herbs, tea, bread and rice is comparatively higher than a typical diet in Western Europe and the US. This might explain the lower homocysteine levels observed in our population as compared to other populations.[29]

According to the lower level of total plasma homocysteine in Iranian population, we expected to obtain lower levels in our study group compared with other countries. But the mean total plasma homocysteine level, neither in cases nor in controls, did not show a significant different compared with other studies. We also failed to find any difference in existence of hyperhomocysteinemia among different ages, where other studies[15] demonstrated more strongly association in patients younger than 70 years old.

The potential importance of treating underlying cardiovascular risk factors is borne out by several reports. Patients with retinal vascular occlusive disease have a significant excess of mortality from coronary and cerebrovascular diseases.[3,33,34] Unlike other risk factors, hyperhomocysteinemia is readily reversible in most individuals with supplying inexpensive vitamin preparations containing folic acid and other vitamins. Vitamin supplementation reduces homocysteine level regardless of the underlying cause.[35,36] Folate supplementation is economical and does not give rise to any major side-effects, raising the possibility that some forms of vascular disease may be easily, safely, and inexpensively treated. It is assumed that by reducing the toxic effect of homocysteine on the blood vessels, the probability of further retinal and systemic vascular occlusion, and therefore the resulting morbidity and mortality will be reduced. It has been shown that homocysteine-lowering treatment significantly reduced the risk of vascular events and other sequels of classical hyperhomocysteinemia.[36,37] However, as it is still controversial, further research to assess this association may be useful. Large-scale randomized trials will be required to confirm that reducing plasma homocysteine levels results in decreased retinal and systemic atherothrombotic vascular disease.

Conclusion

Elevated total plasma homocysteine level is an independent risk factor for CRVO in Iranian population. In addition to an evaluation of all conventional cardiovascular risk factors, measurement of total homocysteine for evidence of hyperhomocysteinemia may be important in the initial investigation and management of patients with CRVO. It is suggested to conduct a study to evaluate effect of lowering homocysteine levels by vitamin supplementation on prevention of recurrence of disease in the same or fellow eye, reduction of other cardiovascular events, and improvement of the prognosis.

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