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VARIATIONS IN THE NATURAL COURSE OF ELEVATED PLASMA HOMOCYSTEINE LEVEL FOLLOWING RETINAL VEIN OCCLUSION AT PRESENTATION.

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ABSTRACT

Purpose: No study has done yet to see the natural course of high homocysteine (HHcys) level following retinal vein occlusion (RVO). Hence our study tried to find out level of Hcys after 1 month of follow up among the RVO with HHcys at presentation. **Material & Methods:** A total of 37 patients with HHcys on the 2nd day of presentation in RVO, were reevaluated for fasting plasma Hcys levels on 30th day in their respective follow up in one year prospective case-control study. No intervention was done to reduce the HHcys during this period. **Results:** Hcys levels were increased significantly in the patients with RVO (mean total Hcys, 18.16 ± 4.73 µmol/L) as opposed to the control subjects (mean total Hcys, 11.05 ± 2.21 µmol/L; $P < 0.001$) on 2nd day of presentation. One month follow up Hcys estimation revealed 22 patients with HHcys (mean total Hcys, 17.16 ± 4.13 µmol/L) and 15 patients with normal Hcys level (mean total Hcys, 11.76 ± 2.93 µmol/L). **Conclusions:** Elevated Hcys is not only a risk factor for RVO but also a marker of acute retinal vein occlusion hence routine therapy of Hcys lowering agents should be done judiciously in retinal vein occusion patients at presentation.

KEYWORDS: Homocysteine (Hcys), Hyperhomocysteinemia (HHcys), Retinal vein occlusion (RVO).

INTRODUCTION

Atherosclerosis induced retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy.[1] The retinal vein and artery share a common adventitial sheath at arteriovenous crossings so that atherosclerotic changes in the artery may compress the vein and precipitate RVO.[2]

Homocysteine (Hcys) is a derived amino acid from dietary methionine. Hcys is either converted back to methionine by B_{12} and folate or metabolized to cystathionine by B_6.[3] Severe HHcys is rare and caused by genetic deficiencies in the enzymes cystathionine β-synthase (CBS) and methyltetrahydrofolate reductase. Mild to moderate HHcys can be caused by deficiencies in nutrients such as B_{12}, B_6 and folate.[4]

Hyperhomocysteinemia (HHcys) is reported as a risk factor for atherosclerosis in coronary, cerebral and retinal vasculature.[5-8] There were reports in support of the hypothesis that HHcys were associated with RVO cases.[9-11] Elevated Hcys level can be lowered by folic acid supplementation.[12] But no study has done yet to see the natural course of high Hcys level following RVO. Hence our study tried to find out level of Hcys after 1 month of follow up among the RVO with HHcys at presentation.

MATERIALS AND METHOD

A 1-year prospective case-control study of consecutive, unrelated, adult patients with a diagnosis of RVO in the absence of any other local or systemic disease was conducted at the Regional Institute of Ophthalmology, Kolkata. Fasting plasma Hcys levels were measured on the 2nd day of presentation to OPD. Patients experiencing any confounding conditions, such as malignancy, sepsis, liver and renal failure, recent cardiovascular and cerebrovascular accidents (<6 months), previous thromboembolic events, inflammatory disorders, thyroid disorder, diabetes, hypertension, glaucoma, dyslipidemia, vitamin intake (B12 and folate), alcohol or drug use (methotrexate, fibrates), food faddists, elevated prothrombin time, elevated activated partial thromboplastin generation time and smoking, were excluded from the study population by detailed history, clinical examination and laboratory investigation. A total of 44 (27 males and 17 females) patients with HHcys were selected in the study. They were reevaluated for fasting plasma Hcys levels on 30th day in their respective follow up. No

intervention was done to reduce the HHcys during this period. Seven (7) patients were lost and 37 completed the study. The people who accompanied the RVO patients were evaluated as controls, based on the same afore-mentioned inclusion and exclusion criteria. The institutional ethics committee approved the study and informed consent was obtained from all study participants, in accordance with the Declaration of Helsinki. Ophthalmic examinations, including visual acuity, fluorescent angiography and dilated retinal examination of both eyes, were used for the clinical diagnosis of RVO. Statistical analysis was performed using the Student's *t*-test and SPSS version 11.5 (SPSS Inc., Chicago, IL, USA). Plasma Hcys was estimated by enzymatic method in semiautoanalyser (ERBA Semiautomated Biochemistry Analyser) with a Reagent kit, supplied by Lilac Clinical chemistry division.[13] (Linearity extends to 50 µmol/L).

RESULTS

The mean age of RVO patients and control participants were 48.1 ± 11.2 years and 52.2 ± 11.6 years respectively. Of the 37 RVO cases 26 patients were BRVO 10 were CRVO and 1 were HCRVO.

Hcys levels were increased significantly in the patients with RVO (mean total Hcys, 18.16 ± 4.73 µmol/L) as opposed to the control subjects (mean total Hcys, 11.05 ± 2.21 µmol/L; P < 0.001) on 2nd day of presentation. (Table- 1) One month follow up Hcys estimation revealed 22 patients (Group-A) with HHcys (mean total Hcys, 17.16 ± 4.13 µmol/L) and 15 patients (Group-B) with normal Hcys level (mean total Hcys, 11.76 ± 2.93 µmol/L). (Table- 2).

Table- 1: Mean plasma Hcys levels in RVO and control subjects on 2nd day of presentation

Parameter	RVO (mean ± SD µmol/L)	Control (mean ± SD µmol/L)
Plasma Hcys	18.16 ± 4.73*	11.05 ± 2.21

'*' P <0.001 as compared with control.

Table- 2: Comparison of mean plasma Hcys levels in RVO between 2nd day and 30th day following presentation

Parameter	2nd day value of all RVO patients (mean ± SD µmol/L)	30th day value of RVO patients in Group-A (mean ± SD µmol/L)	30th day value of RVO patients in Group-B (mean ± SD µmol/L)
Total	37	22	15
Plasma Hcys	18.16 ± 4.73*†	17.16 ± 4.13‡	11.76 ± 2.93

'*' P >0.1 as compared with Group-A.

'†' P <0.001 as compared with Group-B.

'‡' P <0.001 as compared with Group-B.

DISCUSSIONS

Hcys exerts its toxic effect to endothelium by reducing bioavailability of nitric oxide[14], abnormal expression of various thrombotic factors.[15] Hcys is metabolised into hcys-thiolactone that contributes to Hcys toxicity in humans.[16] (Hcys-thiolactone hypothesis) leading to endothelial dysfunction. HHcys can lead to upregulation of the inflammatory response in the vascular smooth muscle cells causing atherosclerosis.[17] HHcys inhibits reverse cholesterol transport by reducing circulating HDL via inhibiting ApolipoproteinA-I protein synthesis.[18]

HHcys was reported as an independent risk factor for RVO.[9] This study also showed that hcys levels were increased significantly in the patients with RVO as opposed to the control subjects ($P < 0.001$). (Table- 1) Plasma hcys levels in 22 group-A patients were remain elevated (mean total Hcys, 17.16 ± 4.13 μmol/L) as no intervention was done to reduce the HHcys during this period but 15 group-B patients had their Hcys level returned to normal (mean total Hcys, 11.76 ± 2.93 μmol/L). (Table- 2) Osorio A et al have observed the Different behaviors of Hcy levels in MI patients (days 0, 2, 5, 7, 9 and 11 post-infarction) and predicted that this might correspond to a history or absence of history of asymptomatic myocardial ischemia.[19] Valjevac A et al have also observed two different patterns of Hcy changes in early post infarction period (Day-2 to day-5) which might reflect two distinct populations of AMI patients. Possible explanation for the observed findings could be a different genetic background, vitamin and oxidative status of patients with AMI.[20] These hypotheses did not hold true in our study. Possible explanation of such variation can be explained by the acute phase reactant property of hcys[21,22] in group-B patients as their levels rise with acute insult and subsidies when the acute phase is over.

From this study we can conclude the elevated Hcys is not only a risk factor for RVO but also a marker of acute retinal vein occlusion hence routine therapy of Hcys lowering agents should be done judiciously in retinal vein occusion patients at presentation.

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