ORIGINAL RESEARCH PAPER

Volume-8 | Issue-1 | January-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

TO EVALUATE HYPERHOMOCYSTEINEMIA, AS A RISK FACTOR FOR RETINAL VENOUS OCCLUSION AND NON ARTERITIC ISCHEMIC OPTIC NEUROPATHY.

Ophthalmology

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ABSTRACT

Purpose: To evaluate hyperhomocysteinemia hHcy as a cause of retinal vascular disease and neurophthalomogy in our hospital.

Materials and Methodology: It is a prospective study done between 2016 and 2018..This study includes 65 young patients,<50 yrs of age who presented in the ophthalmology department with retinal vein occlusions(RVO) and nonarteritic optic neuropathy(NAION) and had no associated systemic or occular disease. In these study 45 patients had RVO and 20 patients were of NAION. All the patients were advised serum homocysteine levels.

Results: 22 patients with RVO and 6 pts of NAION, totaling to 28 came positive for high homocysteine levels and were started on vitamin B6 20 mg, B12 500 µg, folic acid 5 mg and glycine 500 mg along with other supportive treatment. Among the positive patients, 60% (17 cases) had moderate, 32% (9 cases) of patients had intermediate, 2patients (8%) had severe hHcy. Treatment of these cases with vitamin supplementation showed a decrease in fasting serum homocysteine levels by 10 ± 4 µmol/L (range 6-15 µmol/L) after 6 months and resolution of the clinical findings

Conclusion: In all cases of veno- occlusive disorders and NAION, evaluation of homocysteine levels plays an important role. hHcy treated with vitamin B12 and folic acid shows a decrease in the risk of complications. All detected cases of hHcy should undergo an ophthalmic evaluation at the earliest.

KEYWORDS

Hyperhomocysteinemia, Retinal vein occlusions, Nonarteritic ischemic optic neuropathy.

INTRODUCTION

Hyperhomocysteinemia(hHcy) is a medical condition characterized by an abnormally high level of homocysteine in the blood, conventionally described as above 15 µmol/L. It is observed in approximately 5% of the general population. The cause of HHcys is varied. Severe hHcys is due to rare genetic defects resulting in deficiencies of the enzymes cystathionine β-synthase (CBS) and methyltetrahydrofolate reductase. Mild hHcys is due to impairment in the enzymes in a transmethylation pathway associated with or without nutritional deficiencies such as B_{12} and folate [1].

All circulating Hcys is primarily derived from dietary methionine, which acts as a methyl group donor in the form of *S*-adenosyl methionine. On donating the methyl group it forms *S*-adenosyl Hcys which is then converted to Hcys. Hcys is a sulfur-containing nonprotein amino acid that is either metabolized to cystathionine by the transsulfuration pathway, requiring B_6, or it is converted back to methionine by $B_{12}$and folate, requiring transmethylation [2].

Hyper-homocysteinemia(hHcy) is categorized as: moderate (15 to 30 µmol/L), intermediate (30 to 100 µmol/L), and severe (> 100 µmol)based on the serum levels.

hHcy can be associated with increased risk of ocular vascular and neuro-ophthalmology disorders in par with that of cardiovascular and central nervous system diseases[3]) Elevated high levels of homocysteiene is both an independent risk factor for atherosclerotic vascular disease and interacts with other risk factors such as smoking and hypertension to increase cardiovascular disease. hHcy levels are determined by both genetic and nutritional factors and possible mechanisms of action of homocysteine on vascular endothelium include promotion of platelet activation, enhanced coagulability, and smooth muscle proliferation[4]

Retinal venous occlusion (RVO) is one among the most common retinal vascular diseases. It is predominantly of two types, central retinal venous occlusion (CRVO) and branch retinal venous occlusion (BRVO). The basic pathology of the disease is localized atherosclerosis. It is often associated with systemic diseases. In many cases, it also occurs in young adults with no other systemic disease. Both local (raised intra ocular tension) and systemic risk factors (diabetes mellitus, hypertension, hyperlipidaemia) have been associated with RVO [5]. Among the types of RVO, based on the site of occlusion and on the type of consequent vascular damage CRVO have poorer prognosis than the BRVO.

Though hypercoagulability has been reported in the pathogenesis of RVO in young patients, laboratory tests have not accounted for this cause in most of these patients [6].

Among the parameters tested, hyperhomocysteinemia (HHcys) and circulating antiphospholipid antibodies are reported to be significantly more common in the patients with CRVO [7]. Boyd et al. [8] have reported that there is no significant increase in factor VIII (von Wilbrand factor), apart from homocysteine (Hcys) levels in the CRVO cases compared with the control subjects.

Non-arteritic anterior ischaemic optic neuropathy (NAION) is typically a disorder of older patients who have predisposing vascular and structural optic disc risk factors. Occasionally, NAION occurs in younger, non-diabetic patients who do not have the conventional vascular risk factors such as tobacco use, hyperlipidaemia, or hypertension. There have been anecdotal reports of thrombotic tendencies in patients with NAION.(9,10,11) Although NAION is most probably related to local factors compromising the posterior ciliary artery circulation at the optic nerve head (so called “disc at risk”), it is also possible that some systemic factors such as hyperhomocysteinaemia and the MTHFR C677T mutation may enhance local atherogenesis at the level of the posterior ciliary arteries, thereby precipitating the development of NAION in those at risk for the disease.

Increasing number of young patients are now being found to be suffering from vascular diseases and optic neuropathy. Hence this study was conducted to find out the prevalence of hypercystenimia in young patients suffering from vascular diseases and neuropathy.

Materials and method

A 2 year prospective study of consecutive, unrelated adult patients, with a diagnosis of RVO and NAION in the absence of any other local and systemic disease. A total of 65 patients, 45 with RVO and 20 with NAION were enrolled for this study. A detailed questionnaire on family history, social status, and dietary habits, including other habits such as smoking, alcohol intake, history of systemic diseases, other ocular diseases and drug history was completed by all the study subjects. Hypertension, diabetes mellitus, cardiovascular disease, high cholesterol, renal disease, liver disease, hematologic and coagulation abnormalities were ruled out in the present study based on the biochemical and hematologic tests apart from the questionnaire.

Ophthalmic examination of eyes, including visual acuity, relative afferent pupillary defect (RAPD), and fundus examination, was used

for the clinical diagnosis. Of the 45 RVO cases patients were included in the study. Among them 24 had CRVO and 21 had BRVO. All RVO and NAION cases were unilateral. None of the study subjects had any history of major thromboembolic episode.

Measurement of Plasma Hcys

Venous blood samples were drawn into EDTA-containing tubes after the participants fasted overnight. Plasma was separated immediately from blood cells by centrifugation at 1,000×*g* at 25 °C for 3 min and checked for homocysteine levels.

Other biochemical tests, tests for hematologic and coagulation defects, were performed to rule out any systemic disease.

hHcy was defined as having a serum level >15 µmol/L.It is further categorized as moderate, intermediate, and severe if the level was 16-30, 31-100, and more than 100 µmol/L, respectively

RESULTS

Of the 65patients 38were male patients and 27 were females. The mean age group of presentation was 34.8 years (ranging from 19 years to 50 years).

In the study group, 45 patients were of RVO(27 CRVO and 18 BRVO)and 20 patients had NAION.

The following table shows the presence of homocystenimia in the patients

Table 1: showing the homocysteine levels in the total study

	CRVO	BRVO	NAION
hHcy +	15	7	6
hHcy -	12	11	14
total	27	18	20
Positive %	55.55%	38.88%	20%

Thus it is seen that a total of 22(48.8%) patients in RVO group and 6(30%) in NAION group had high serum homocysteine levels.

Out of the 28patients with hHcy, 32% (9 cases) of patients had intermediate hHcy, 60% (17 cases) had moderate hHcy and 8%(2 cases) had severe hHcy

Table 2: shows the severity of homocysteinemia in the positive cases

hHcy grades	No of cases	percentage
moderate	17	60%
intermediate	9	32%
severe	2	8%

DISCUSSION

Our study shows a high prevalence of hyperhomocystenemia about 48.8% in retinal vacular disease, more so in CRVO group as compared BRVO. This is in concurrence with other studies. Lattanzio et al. [12] have reported an OR of 3.0 for fasting HHcys in patients with CRVO and an OR of 1.3 was reported by another study in a Chinese population [13]. The meta-analysis by Janssen et al. [14] has also shown an overall OR of 8.9 (95 % CI, 5.7–13.7) for Hcys. The meta-analysis by Cahill et al. [15] has shown that the retinal vascular occlusion is associated with elevated plasma Hcys levels and low serum folate levels.

There have been anecdotal reports of thrombotic tendencies in patients with NAION[16-18] . The relation of hyperhomocysteinaemia to NAION remains unclear. Pianka et al[19] reported elevated levels in 45% of 40 NAION patients (mean age 66 years) v/s 9.8% of controls, and Wegeret et al[20] also reported mean elevation (11.8 v/s 9.8 µmol/l) in 59 NAION patients v/s controls,SIMILARLY our study showed a prevalence of 30%pts with NAION HAVING Hhcy.However . Biousseet al[21] reported normal values in 14/14 patients with a mean age of 43 years.

NAION is most probably related to local factors compromising the posterior ciliary artery circulation at the optic nerve head (known as the "disc at risk"). It is possible that systemic factors such as hyperhomocysteinemia may enhance local atherogenesis at the level of posterior ciliary arteries, thereby precipitating the development of NAION[20,21].

Ocular complications are seen at all levels of hyperhomocystenimia, most been seen at even moderate levels,as in our study.

High levels of plasma homocystine are toxic to the vascular endothelium, presumably by directly injuring the vessel's endothelium by the release of free radicals, creating an environment of hypercoagulability, and by modifying the vessel wall(.16) A unique aspect of hypercoagulability associated with hHcy is that homocysteine levels can be decreased simply by administrating vitamin B12 (100 mcg/day), vitamin B6 (3 mg/day) and folate (400 mcg/day).17,18 .These three vitamins are important cofactors in the processing and conversion of homocysteine to either methionine or cysteine. Our patients too were treated with folic acid 5 mg in combination with 20 mg pyridoxine, mecobalamin 500 mcg and 500 mg glycine (tab homocyst). Along with this patient were given specific treatment for their ocular manifestations.

CONCLUSION

hHcy can be the cause for venous stasis causing various ocular manifestation. In all cases of veno occlusive disorders and NAION, evaluation of homocysteine levels plays an important role. If high homocysteine levels are detected treating them with vitamin B12 and folic acid can reduce the pathological role of homocysteine, thereby reducing the vascular catastrophes of ocular and other systems. It also reduce the severity and frequency of future complications of hHcy. All detected cases of hHcy should undergo ophthalmic evaluation for early detection of the various manifestations and their prevention.

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