Original Article

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Ocular Manifestations of Hyperhomocysteinemia and their Response to Therapeutic Modalities

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Abstract

Introduction: Hyperhomocysteinemia (hHcy) is observed in approximately 5% of the general population. 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.

Purpose: To evaluate the ocular manifestations of hHcy and their therapeutic response to treatment.

Materials and Methodology: It is an interventional study done between June 2012 and February 2015. This study includes the (1) patients with hHcy referred from other departments for ophthalmic evaluation, (2) the patients who presented in the ophthalmology department with various vascular and neuro-ophthalmology findings associated with hHcy. All the patients with hHcy with ocular manifestations were started on vitamin B6 20 mg, B12 500 µg, folic acid 5 mg and glycine 500 mg along with other supportive treatment. Their serum homocysteine levels were repeated after 6 months.

Results: Out of 59 cases of hHcy 25 patients (42.3%) showed ocular findings such as branch retinal vein occlusion, papilledema, visual field defects, non-arteritic anterior ischemic optic neuropathy and optic disc pallor. Among the patients with ocular manifestations 32% (8 cases) of patients had intermediate, 60% (15 cases) had moderate and 2 patients (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 in vaso occlusive disorders and papilledema. Out of the 7 neuro ophthalmology patients 2 patients showed worsening of the neurological defects.

Conclusion: hHcy treated with vitamin B12 and folic acid shows a decrease in the risk of hHcy complications. All detected cases of hHcy should undergo an ophthalmic evaluation at the earliest.

Key words: Branch retinal vein occlusion, Hyperhomocysteinemia, Non-arteritic anterior ischemic optic neuropathy, Optic disk pallor, Papilledema, Visual field defects

INTRODUCTION

Homocysteine, an intermediate in the methionine metabolism, if increased in the plasma can produce an increased risk of thrombosis and endothelial defect.[1] S adenosyl methionine, a biochemical precursor, is involved in transfer of one carbon (methyl) groups during many biochemical synthesis. S adenosyl methionine is synthesized from the amino acid methionine by a reaction that includes the addition of methyl group and purine base (from ATP). When S adenosyl methionine donates methyl group for the synthesis of thiamine, choline, creatinine, epinephrine, protein and DNA methylation it is converted to S adenosyl homocysteine. After losing the adenosyl group the remaining homocysteine can either be converted to cysteine by vitamin B6 dependent trans sulfuration pathway or converted back to methionine in a reaction that depends on folate and vitamin B12. When either folate or vitamin B12 is lacking the homocysteine to methionine reaction is virtually blocked causing homocysteine to build up in the effected tissues and spill into circulation. Vitamin B6 dependent transulfuration

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pathway can metabolize excess homocysteine.[2] Although the homocysteine plays an important role in synthesis of methionine the bulk of current research suggest that when the cellular homocysteine leaks into circulation even in slight elevated amounts the risk of coronary heart disease, peripheral vascular disease, venous thrombosis and pulmonary embolism increases. The mechanism of effects of homocysteine on atherogenesis are not known.[2] Thus, serum levels of folate, vitamin B6 and B12 levels are inversely related to the plasma total hyperhomocysteinemia (hHcy) levels. hHcy can be either acquired or inherited type. Inherited hHcy occurs due to various causes mainly - cystathionine β synthase, methionine synthase and 5-methytetrahydrofolate reductase deficiency.[3]

hHcy is observed in approximately 5% of the general population and is associated with an increase in risk of many disorders, including vascular and neurodegenerative diseases, autoimmune disorders, birth defects, diabetes, renal diseases, osteoporosis, neuropsychiatric disorders and cancer.[3] The thrombo embolic effect of raised total plasma homocysteine level has been documented as early as 1968.[4] The idea that elevated homocysteine was associated with arterial thrombotic disease was first put forth in 1969.[5] The risk of venous thrombotic disease in patients with hHcy was first addressed in 1991.[6] Possible mechanisms by which homocysteine may contribute to thrombosis include activation of factor V, increased oxidation of low-density lipoprotein, and inhibition of plasminogen activator binding and of protein C activation, or direct damage to the vascular endothelium.[7]

In the ocular system, many lines of evidence indicate that hHcy is a risk factor in a variety of disease including retinal arterial atherosclerosis, macular degeneration and optic atrophy due to retinal micro vascular occlusions, non-arteritic ischemic optic neuropathy (NA-ION), cataract, glaucoma and exudative age related macular degeneration.[8]

The primary goal of treatment is to lower blood levels of homocysteine to normal. Therapy with folic acid, vitamin B6, and vitamin B12 has been shown to lower homocysteine levels and may prevent occlusive disease. Vitamin treatment was associated with a significant fall in thrombin-antithrombin III complexes and prothrombin fragment 1 + 2 concentrations in peripheral venous blood.[9] Supplementation of folic acid, vitamin B12, and vitamin B6 can efficiently lower plasma hcy levels, in most patients, regardless of the underlying cause.[10,11] Further folic acid supplementation improves arterial endothelial function in adults with relative hHcy, with potentially beneficial effects on the atherosclerotic process. Daily folate and vitamin B12 supplements of 500 μg or less can reduce plasma total homocysteine levels up to 15%.[12,13] Furthermore, anticoagulant medications may be added to treat and prevent thrombosis.

In this study, we treated and followed up hHcy patients with ocular manifestations and observed their response to the treatment.

MATERIALS AND METHODOLOGY

This interventional study was conducted between June 2012 and February 2015 in Kempegowda Institute of Medical Sciences and Research Centre, Bengaluru India. Ethical Clearance for this study was obtained from the Institutional Ethical Committee and Helsinki guidelines were followed during this study. Informed consent was obtained for all the patients or from the attendants' who were included in this study. Patients included in this study were cases of branch retinal vein occlusions (BRVOs) associated with hHcy, papilledema with hHcy and referred cases of hHcy for ophthalmology opinion from medicine, neurology and cardiology department with systemic manifestations like hemiplegia, gait abnormalities, headache, vomiting, cardiovascular diseases and coma. hHcy was defined as having a serum level >15 μmol/L. It was further categorized as moderate, intermediate, and severe if the level was 16-30, 31-100, and more than 100 μmol/L, respectively. Serum homocysteine levels were estimated using enzymatic recycling method. Visual acuity was tested by Snellens chart. The best corrected visual acuity was recorded. If the person could not correctly recognize the top letter of the chart, visual acuity was noted using the finger counting method at various distances. Anterior segment evaluation was done using slit lamp and refraction was done by using Huwitz autorefractometer. Intraocular pressure was recorded using Perkins tonometer. Posterior segment evaluation was done after dilating with tropicamide - phenylephrine eye drops using indirect ophthalmoscope (Keeler), 90 D panfundoscopy lens and Goldmann 3 mirror examinations. Visual field analysis (where possible) was done using humphrey visual field analyzer. In selected cases, we performed fluorescein angiography. Other investigations like radiological investigations such as computed tomography, magnetic resonance (MR) imaging (MRI), MR venogram, and lumbar puncture were reviewed from the records. Hematological workup such as lipid profile, hemogram, biochemistry and serology were reviewed.

All the cases with ocular manifestations were treated with tablet homocyst (vitamin B6 20 mg, B12 500 μg, folic acid 5 mg and glycine 500 mg) along specific treatments like oral acetazolamide 1-g/day in cases of papilledema, injection heparin 5000 IU intravenous 6th h for 1-week

with oral acenocoumarol 2-3 mg OD starting on day 6 in cases of cerebral venous thrombosis, intravitreal bevacizumab 1.25 mg/0.05 ml for branch retinal vein and vein occlusions, oral steroids 1-mg/kg/body weight for 2 weeks then tapered along with oral pentoxyphyllin 400 mg once a day for NA anterior ION (NA-AION), oral anticoagulants aspirin 150 mg with clopidogrel 75 mg OD along with atorvastatin 20 mg OD for patients with ischemia or infarcts. All the patients were followed up for a period of 6 months - 2 years. Serum homocystein levels were measured again after 6 months.

RESULTS

Totally 59 patients with hHcy underwent ophthalmological evaluation. Out of this 40 (67.8%) were male patients and 19 (32%) were females. The mean age group of presentation was 34.8 years (ranging from 19 years to 60 years). 54.3% of the patients had additional co morbid conditions diabetes and hypertension. 45.7% (27 patients) presented with headache and giddiness, 37.3% (22 patients) presented with various visual disturbances like detective vision, field loss and 17% (10 patients) had no-ocular symptoms. 42.3% (25 patients) showed ocular findings such as BRVO, papilledema, visual field defects, NA-ION and optic disc pallor and 57.6% (34 patients) had no ocular findings.

Out of the 25 patients with ocular morbidities with hHcy 32% (8 cases) of patients had intermediate hHcy, 60% (15 cases) had moderate hHcy and 2 patients (8%) had severe hHcy (Table 1a and b). Table 2 shows the various ocular manifestations of hHcy with respect to their serum levels.

All patients 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. Patients were followed up for a minimum period of 6 months to 2 years and their response to treatment was observed. The response of the various manifestations to treatment is listed in Table 3.

Table 1a: Severity of hHcy

hHcy	Number of cases	Percentage	Levels (μmol/L)
Moderate	26	44.1	19-28
Intermediate	29	49.1	35.5-58
Severe	4	6.8	100-115
Total	59	100	

hHcy: Hyperhomocysteinemia

Table 1b: Severity of hHcy in patients with ocular morbidities

hHcy	Number of cases	Percentage
Moderate	15	60
Intermediate	8	32
Severe	2	8

hHcy: Hyperhomocystinemia

Serum homocysteine levels, of 23 patients with ocular manifestations due to hHcy on treatment, were repeated after 6 months. There was a decrease in fasting serum homocysteine levels by 10 ± 4 μmol/L (range 6-15 μmol/L). One patient was lost during follow-up and one patient died due to neurological complications. Table 4 compares the levels of homocysteine before and after treatment after a period of 6 months.

DISCUSSION

hHcy is reported as an independent risk factor for systemic and ocular vasoocclusive disorders, including NA-ION, central retinal artery occlusion, and central retinal vein occlusion, especially in young patients.[14,15]

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] There are other conditions that may increase plasma homocystine levels: Age, gender, renal failure, medications, and decrease in uptake of vitamins B6, B12, and folic acid. 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. Recent studies have demonstrated that oral folic acid in a daily dose of 1-10 mg consistently reduces Hcy levels by 10-20%.[19-21] It is assumed that by reducing the toxic effect of homocysteine on the blood vessels, the probability of decreasing the disease course and resolution of the manifestations can occur and can prevent further vascular occlusions, therefore the resulting morbidity, will be reduced.

However, in a few studies low levels of serum folate, but not vitamin B12, have been associated with retinal vascular occlusive disease due to hHcy.[22-25] vitamin B6 is primarily a cofactor in the transsulfuration pathway of homocysteine metabolism, and its effect on lowering plasma tHcy levels may only be apparent after methionine loading. Nevertheless, all three of these supplements are inexpensive, available over the counter, and combined

Table 2: Ocular presentations of hHcy with their levels

Manifestation	Numbers	%	Moderate	Intermediate	Severe
Papilledema (CVT, BIH)	6	12.2	4	2	0
Branch retinal vein occlusion	10	20.4	6	3	1
NA-AION	2	4.1	2	0	0
Temporal optic disc pallor (MCA or PCA occlusion)	4	8.2	3	0	1
Normal fundus with field defects (infarcts in temporal/parietal/occipital lobe)	3	6.1	0	3	0
Normal no ocular manifestations	34	57.6	11	21	2

NA-AION: Non-arteritic anterior ischemic optic neuropathy, CVT: Cerebral venous thrombosis, BHI: Breath-holding index, hHcy: Hyperhomocystinemia

Table 3: Manifestations of hHcy with the treatment given and its response

Manifestations	Treatment given	Response to treatment after 6 months
Papilledema (CVT, BIH)	Tab homocyst along with tab acetazolamide 1-g/day till symptomatically better. For patients with CVT injection heparin 5000 IU IV 6th h for 1-week with oral acenocoumarol 2-3 mg once daily starting on day 6 till life long	Patients with CVT had a good response to treatment with complete resolution of papilledema after 6 months. However, patients with BIH had resolutions of symptoms but not complete resolution of papilledema in 50%
Branch retinal vein occlusion	Tab homocyst along with intravitreal bevacizumab 1.25 mg/0.05 ml	Fundus examination revealed good response to treatment with no reoccurrences
NA-AION	Tab homocyst along with oral steroids 1 mg/kg/ body weight for 2 weeks then tapered along with oral pentoxifylline 400 mg once a day	There was improvement in the visual acuity by 1 line in one case, but defect persisted. No reoccurrences
Temporal optic disc pallor (MCA or PCA occlusion)	Tab homocyst along with oral anticoagulants aspirin 150 mg with clopidogrel 75 mg OD along with atorvastatin 20 mg OD lifelong	One patient despite all treatment died during the study period due to repeat CVA
Normal fundus with field defects (infarcts in temporal/ parietal/occipital lobe)	Tab homocyst along with oral anticoagulants aspirin 150 mg with clopidogrel 75 mg along OD with atorvastatin 20 mg OD lifelong	Field defects persisted one patient despite oral anticoagulant had another episode of stroke

CVT: Cerebral venous thrombosis, CVA: Cerebrovascular accident, NA-AION: Non-arteritic anterior ischemic optic neuropathy, BHI: Breath-holding index, hHcy: Hyperhomocystinemia, IV: Intravenous

Table 4: Comparison of the serum homocystine levels before and after treatment

hHcy levels	Number of patients before treatment	Number of patients after treatment
Moderate	14 (19-28 μmol/L)	18 (13-29 μmol/L)
Intermediate	8 (35.5-58 μmol/L)	5 (30-86 μmol/L)
Severe	1 (102 μmol/L)	0
Total patients	23	23

hHcy: Hyperhomocystinemia

folate and B12 supplementation would avoid the theoretical risk of neuropathy secondary to unopposed folate therapy in B12-deficient patients.[26]

This study shows that there was a decrease of 10 ± 4 μmol/l in serum homocysteine levels following supplementation of vitamins. As our patients were started and maintained with full dose of vitamin supplementation clinical presentations such as venous and cerebral sinus thrombosis and papilledema resolved over a period of 6-8 months and did not show new presentations of Hhcy in eye in 2 years follow-up.

In our study, we came across 6 patients with papilledema and hHcy, 4 of which had a normal MRI and the other 2 had venous sinus thrombosis diagnosed on MR venogram (4 moderate and 2 intermediate). A study done by Martinelli *et al.*[27] shows that hHcy increases the risk of cerebral vein thrombosis by approximately 4-fold. The other possible mechanism which can cause papilledema in a case of hHcy can be due to increase viscosity of blood in the veins leading to venous stasis and papilledema. In the present study, 7 patients with neuro ophthalmology manifestations such as disc pallor and field defects showed previous or present cerebral vascular catastrophes' involving optic tract and radiations. Out of this one patient developed progressive vascular thrombosis and succumbed in spite of all medical treatments. Another patient developed cerebro vascular accident in the course of treatment and recovered.

CONCLUSION

hHcy can be the cause for venous occlusive disorder and venous stasis causing various ocular manifestation. In all cases of veno occlusive disorders and atherosclerosis 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 reduces

the severity and frequency of future complications of hHcy. In all cases of hHcy should be supplemented with lifetime vitamin B12 and folic acid as in our study showed the fall of homocysteine levels following treatment. All detected cases of hHcy should undergo ophthalmic evaluation for early detection of the various manifestations and their prevention.

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