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Hyper Homocysteinemia in Ocular Diseases - A Study

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Abstract

Homocysteine is a derived sulfur, non-proteinogenic amino acid (1). Hyperhomocysteinemia is a risk factor for vascular and neurodegenerative ocular diseases eg retinopathies, glaucoma, maculopathies, cataract.

Optic neuropathy and retinal vascular diseases. This is because of impaired vascular endothelial function, apoptosis of retinal ganglion cells and oxidative stress (2).

Hyperhomocysteinemia poses metabolic disorder in which there is high level of homocysteine caused by deficiency of cystathionine- beta synthase, metiionine synthase, vitamin B6 and B12 (3).

Patients may supplement with these vitamins to lessen the ocular morbidity.

This article discusses the association of hyperhomocysteinemia in ocular problems and possible mechanism in pathogenesis which may help in proper management.

Keywords: Hyperhomocyseinemia; diabetic retinopathy; Glaucoma; Optic neuropathy; Cataract; Vit B12

Introduction

Prevalence of Hyperhomocysteinemia depends on the type of population, age group, dietary pattern and genetic background (4). It is 5 % in healthy individuals 92.85 % in males and 81.60% amongst females. Homocysteine levels are relatively stable through the first 4 decades of life and then rise sharply after the age of 70yrs(5). Pregnency lowers homocysteine level, renal diseases increase homocysteine level. Coffee consumption of 4 or more cups per day raises Hcy level. Protein consumption more than75gm/day lowers the Hcy levels. Certain drugs also raise the Hcy level.

Genetic Association

Elevated homocysteine is associated with increased risk of ocular morbidity along with other systemic morbidities. Lifestyle eg smoking contribute to high homocysteine levels. It may be high in renal problems, hypothyroidism and deficiency of choline, taurine and acetyl cysteine (5). Homocystinuria is inherited in an autosomal recessive manner, each parent must be a carrier and each of their children has25% chances of being affected, 50% of being an asymptomatic carrier and 25% chances of being unaffected and not a carrier (5). Therefore it is important to test siblings of children who has problem (6).

Homocysteine Formation

Homocysteine is created as a result of the metabolism of proteins, levels are high in people who eat lots of meats and few fruits and vegetables. When proteins are digested, a number of amino acids are liberated. One is methionine, which supports the cellular activities for this activity it takes methyl group from vit B 12 and folic acid. If folic acid and B6 levels are inadequate, then the changed methionine remains as homocysteine (6). There is multitude of diseases in the elderly associated with hyper homocysteinemia eg: ocular diseases, heart failure, stroke, dementia and bone fractures (7).

High plasma Hcy concentration with low folate and B6 are associated with an increased risk of extracranial carotid artery stenosis(8). The impaired endothelial dependent vasodilatation due to elevation of plasma Hcy level prone to vascular diseases. It leads to oxidative damage to the vascular endothelium and proliferation of vascular smooth muscles which contributes to prothrombosis leads to premature arteriosclerosis.

Causes of Hyperhomocysteinaemia (9)

Association of Hyperhomocysteinia in Ocular Morbidities (10).

Hyper homocysteinemia has been implicated in visual dysfunction, as a risk factor for variety of ocular problems eg glaucoma, exudative ARMD, retinal arteriosclerosis, ischemic optic neuropathy and macular and optic atrophy. Menifeststions in eyes are as follows

DRY EYE

Constitute a group of autoimmune disorder(11) due to inflammatory or non inflammatory conditions affecting conjunctiva and tear film. The level of Hcy in the blood raised significantly in patients of dry eye. In Bahcet's disease, serum homocysteine mean levels are considerably high.

Marfan's Syndrome (12)

A rare genetic disorder, affects connective tissue through out body. Presents as hyperhomocysteinaemia, long slender fingers, lens dislocation and defective near vision.It may be associated with high myopia, papillary block, glaucoma and retinal detachment.

Glaucoma

Increased level of Hcy may increased intracellular level of Hcy can increase arterial pressure which alters ocular perfusion pressure leads ti raise intraocular pressure. Patients with pseudo exfoliation and high homocysteine level(13) have an increased prevalence of high IOP. Homocysteine contributes to glaucoma by altered flow dynamics with in ophthalmic and retinal arteries of patient, an association between glaucoma and vascular disease accelerate the glaucomatous process in the presence of nocturnal hypotension.

Pseudoexfoliation Glaucoma

It shares many common associations with hyperhomocystainaemia. Cardiovascular diseases, oxidative stress and Alzheimer's disease(14) are common to both. Exfoliation material contains laminin, elastin and fibrillin, components of extracellular matrix metabolism under the influence of homocysteine.

Primary Open Angle Glaucoma

Homocysteine is a neurotoxin that can induce glaucomatous optic neuropathy, apoptosis of RGCs, extracellular matrix alteration, proinflammatory cytokins and vascular dysregulation.

In primary open angle glaucoma, elevated Hcy level suggests that thermolabile methyl-netetrahydrofolate reductase deficiency may be in part the cause of increased Hcy.Hyperhomocysteinemia noticed in aquous humor and plasma of glaucomatous patients had, POAG, neovascular glaucoma, pigmentary glaucoma, congenital and uveitic glaucoma (15).

Pathogenesis of HHcy associated glaucoma involve several factors; nictinamide(NAM) (16).

NRF2, endoplasmic reticulum (ER), mitochondria and the N-methyl-D-aspartate receptor. Acute Hcy exposure on retinal layers leads to decreased viability of ret. Ganglion cells. This in combination with Hcy upregulating an NRF2- antioxidant pathway, suggests NRF2 is associated with glaucoma.

It is evident that Hcy mediated stimulation of NMDA receptor causes RGC death. Hence Hcy serves as causative agent for glaucoma than a biomarker (17).

More than 70 million people are affected by glaucoma (18). HHcy may interact with glaucoma- relevant genetic and environmental factors contributing to the development of glaucoma. An understanding of the mechanism behind HHcy and glaucoma, may help to slow the prevention, management and slow progression of disease.

Diabetic Retinopathy

Hyperhomocysteinemia has emerged as a great risk factor for development and progression of diabetic retinopathy(19). Defeciency of vit B12 and folate has been associated with increased serum homocysteine level, hence hyperhomosysteinemia proves to be a risk factor for diabetic retinopathy (20).

Prevalence of hyperhomocysteinemia as well as mean serum level of homocysteine were found to be higher in the cases with PDR. Homocysteine is toxic to the vascular endothelium, induces thrombosis and thus aggravates the hypoxic state results in closure of capillary bed. Hence higher concentration of homocysteine in diabetic patients play a role in accelerating microvascular retinal changes. Its concentration is more in proliferative retinopathy in comparison to nonproliferatuve (21).

Nerve Palsy

Hyperhomocysteinemia has emerged as a risk factor for systemic and ocular vaso-occlusive disorders.

Isolated third and sixth cranial nerve palsy reported in few patients where hyperhomocysteinemia was the only risk factor (22).

Implication of Hyperhomocysteinemia in Blood Retinal Barrier Dysfunction

HHcy impairs the function of both outer and inner blood retinal barrier, which is a hallmark of vision los in DR and AMD (23). Elevated Hcy disrupts inner and outer BRB integrity, increases the BRB permeability and disrupts the structural and functional integrity of retina. Leads to retinal ischemia, neovascularisation and vascular leakage.

Retinal Vasculitis

Changes seen in retinal vasculature at an early stage may be due to inflammatory cells causing damage to retina, which disrupts the BRB leading to retinal and vitreous hemorrhage. Defective homocysteine metabolism causes formation of the reactive oxygen and degradation of glutathione resulting indamage of retinal vessels. Direct endothelial cell damage develop as a result of interaction between homocysteine and lipoprotein (24) Hyperhomocysienemia occurs in cases of retinal vasculitis.

Retinal Vascular Occlusive Disease

A moderately raised Hcy in plasma may cause arteriosclerotic vascular diseases. It includes.

Retinal Vein Occlusion

Raised Hcy, activates the factor V, which increases the oxidation of LDL, inhibition of plasminogen activator and the actvation of protein c (25). Hcy produces risk factor in several ways, as –

1. Metabolites can combine with LDL- cholesterol, macrophage in arterial intima result to atherosclerotic plaque (26).
2. Hcy, may activate inflammatory responses leads to aggregation of monocytes to the arterial wall (27).
3. Hcy may dysregulate lipid metabolism in vascular cells through actvation of sterol regulatory elemant – binding protein (28).
4. Hyperhomocysteinemia increases smooth muscle cell proliferation and produce endothelial damage through free radicals (29).

It is evident that HHcy shows 4-5 fold increase in the overall risk for developing RVO (30).

Retinal Artery Occlusion

Hcy induced endothelial cell dysfunction, apoptosis and proliferation disorders are exacerbated (31).

Hcy increases inducible nitric oxide synthase and decreases glutathione level indicates oxidative –nitrosative s, stress. It promotes the expression of profibrogenic cytokins and influences the matrix metalloproteinase and tissue inhibitor of metalloproteinase. MMP degrades collagen, migrates smooth muscle cells with in a vessel and leads to vascular remodeling (32).

It is to conclude that hyperhomocysteinemia predisposes to the development of premature retinal vein and artery occlusion (33).

Ischemic Optic Neuropathy

Mild hyperhomocysteinemia is a risk factor for atherothrombotic diseases as retinal vascular occlusion, non arteritic ischemic optic neuropathy. Low intake of vit B elevates homocysteine. Non arteritic ischemic optic neuropathy is an infarct of optic nerve head, caused by an insufficient blood supply to posterior ciliary arteries, hyperhomocysteinemia is suggested to be a risk factor.

Bilateral painless vision loss is often associated with central or centrocecol scotoma is due to vit 12 deficiency may be associated with HHcy (34).

Conclusion

Direct association of hyperhomocysteinemia with ocular morbidities is established. Homocysteine induced vascular injury, alteration in extracellular matrices, remodeling as well as neuronal toxicity, retinal and lens proteins are liable to be attacked by oxidative stress due to hyperhomocysteinemia.

In view of above, the concentration of homocysteine in plasma may be controlled by periodical evaluation, and morbidity can be prevented by careful management of risk factors eg life style, vitamin intake, proper control of co morbidities, as diabetes, hypertention, dyslipedemia, IOP etc, especially occlusions in young patient should be investigated for embolic phenomena and thrombotic diseases. Hyperhomocysteinemia predisposes to ocular morbidities may need homocystein lowering therapy for prevention.

References

1. Thekkuttuparambil A. Ajith cl.ch, acta 450 (2015): 316-321.
2. Ramakrishnan S., et al. Ind j biochem, Biochem of homocysteine (2006).
3. MP Mattson., et al. folate and homocysteine metabol. Trends neurosc (2003).
4. W Refai., et al. clinic. geritr. Med (1999).

5. AD Wright Martin and PM Dodson. eye 22 (2008): 989-993.
6. M.Goldstein, Leibovitch EYE 18 (2004): 460-465.
7. Ward Dean. https://www.vrp.com N.Y.2003-2004.
8. S Bleich J Roedl., et al. A M. Journal of oph (2004).
9. Sekeryapan B, Oner V, Kirbas A cornea 32.5 (2013): e94-6.
10. Dennis j Dietzen and Marwan Shinwi. clinical chem (2010).
11. Claudio bucolo, Joshua Washington and Robert Ritch. int .j.Moi sci 24.13 (2023): 10790.
12. Mustafa R. kadhim (2011).
13. J Roedl., et al. Pseudoexfoliation glaucoma Am. J.OPH (2004).
14. CI Clement., et al. Plasma homocysteine, MTHFR gene mutation and open angle glaucoma (2009).
15. SJ Loomis., et al. JAMA Ophthalmology (2014).
16. Asaad A Ghanem., et al. current eye research 37.8 (2012).
17. Amany Tawfik., et al. J. CLIN.med 8.1 (2019): 121.
18. Bennett GH., et al. diabetic Retina screen Ir med. J 110 (2017): 628.
19. Malaguarnera G., et al. Biomed Res Int (2014): 191497.
20. Ganapathy PS., et al. Investig. Ophthalmo. Visc sci 50 (2009): 4450-4470.
21. Beard RS., et al. blood (2011).
22. Ali K., et al. The course of retinal vasculitis, The Br. J. of ophthalmology 98.6 (2014): 785-789
23. Mark Cahil., et al. Br, J. of Oph 84 (2000): 154-157.
24. Kapil D Lahiri., et al. Indian. j clin Biochem 28.1 (2013): 61-64.
25. Pianka P, Almog Y, Man O,OPHTHALM 107 (2000): 1588-1592.
26. Clare shute. BMC OPPH 18 (2018): 220.
27. A Niro., et al. J.Med case Rep (2018).
28. Dhipak Arthur., et al. Oman j. ophth 15.1 (2022): 6-12.