Association of Plasma Homocysteine with Risk of Neovascular Age Related Macular Degeneration

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ABSTRACT

Introduction: Hyperhomocysteinemia has been linked with the development of Neovascular age-related macular degeneration (NVAMD) for over two decades. It is a major cause of irreversible blindness in elderly. Homocysteine level estimation and supplementation of Vitamin B12 and Folic Acid has become a conventional norm with retinologists. The evidence for this association is not well established, especially in Indian population. The study aims to fill this knowledge gap by comparing two data sets spaced ten years apart to find any temporal changes in homocysteine levels in Indian population and association with NVAMD.

Material and methods: A cross sectional study was carried out among patients attending Eye OPD of a tertiary care eye centre for two data sets, first between 2007 to 2009 (DS1) and second between 2019-2020 (DS2). Patients were categorised into Neovascular AMD and Non Neovascular AMD on basis of clinical picture, fundus fluorescein angiogram and optical coherence tomography. Plasma homocysteine levels of patients each of Neovascular AMD, Non Neovascular AMD and age matched controls were measured. The normal range of fasting plasma homocysteine for the prescribed laboratory test was 5-15 micro mol/litre. The results of the three groups were collated, tabulated and analysed using analysis of variance (ANOVA) on logarithmically transformed homocysteine level.

Results: The mean homocysteine value in the Neovascular AMD group was 17.94 micromol/l and 18.03 micromol/L in DS1 & DS2 respectively. The mean homocysteine value in the Non Neovascular AMD group was 11.66 micromol/land 11.53 micromol/l, while in control group it was 10.97 micromol/l and 10.88 micromol/l for DS1 & DS2 respectively. The mean plasma homocysteine value in the Neovascular AMD group was higher and statistically significant when compared to the values in the other two groups in both DS1 & DS2.

Conclusion: There exists an association between an elevated plasma level of homocysteine and neovascular AMD, but not with non-neovascular AMD. This association has not been affected significantly by changes in Indian diet and lifestyle over the previous decade.

Keywords: Neovascular Age Related Macular Degeneration, Hyperhomocysteinemia, Nutritional supplementation

INTRODUCTION

Age related macular degeneration (AMD) is a leading cause of blindness in the world in persons older than 60 years of age.[1] Population based studies reported 1.8-4.7% prevalence of AMD in elderly Indian population.[2] The disease is classified into two types, non-neovascular type which forms 85-90% and a wet, exudative or neovascular type which constitutes 10-15% of all the cases of AMD, both of which may give rise to visual loss. The vast majority of people with severe vision loss (20/200 or worse in either eye) from AMD have the neovascular form.[1,3]

In non-neovascular AMD, ophthalmoscopy reveals subretinal deposits called drusens or retinal pigment epithelial (RPE) irregularities, including hyperpigmentation or hypopigmentary changes. Larger drusens may evolve into RPE detachments, geographic atrophy and less frequently neovascular AMD. The wet form of AMD is characterized by the presence of choroidal neovascularization (CNV) and associated manifestations such as retinal pigment epithelial detachment (PED), retinal pigment epithelial tears, fibrovascular disciform scarring, and vitreous haemorrhage.[4]

The proposed multifactorial aetiology of age related macular degeneration leaves multiple unanswered questions about cause and effect relationships of various factors. Major risk factors include age and heredity. Hypertension, high levels of serum cholesterol and high body mass index are accepted systemic risk factors and tobacco smoking is an important environmental exposure factor.[5] In Neovascular AMD there is neovascular proliferation that grows through a break in Bruch's membrane and grows laterally in the subretinal and sub RPE space.[6] Even though this macroscopic effect is well established, the pathogenesis remains unproven with the most accepted theory of an increase in pro-angiogenic factors and a decrease in anti-angiogenic factors. This stimulation for angiogenesis is proposed to be caused by a complex interplay of various inflammatory mediators. The stimulus for this inflammation arising from increased

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oxidative stress, autoimmune processes, dietary deficiencies and light exposure.[3,4,6]

Homocysteine has been demonstrated to be an independent risk factor for atherosclerosis, cerebrovascular and cardiovascular disease.[7] Hyperhomocysteinemia increases the oxidative stress in cells, induces endothelial injury, promotes vascular smooth muscle proliferation and alters vascular coagulant mechanisms.[8,9] It is possible that changes in vasculature and antioxidant stress because of hyperhomocysteinemia may increase the risk of retinal pigment epithelial (RPE) cell damage and cause AMD. The association of elevated plasma levels of homocysteine and AMD has been a subject of multiple studies[10,11,12], with an aim to yield potential therapeutic targets.[7,13,14] The authors conducted a thesis on the subject in 2008 and concluded a statistically significant relationship between plasma homocysteine levels and AMD. However, the understanding of the relationship between homocysteine and AMD advanced over the past decade.[9,15,16,17,18] We tried to replicate our research after ten years with better study design to overcome the limitations of our initial study. Though studies on homocysteine and AMD have been published from India earlier[19], the present study adds to the current scientific knowledge in terms of larger sample size and replication of the study after a duration of ten years.

MATERIAL AND METHODS

A cross sectional study was carried out among patients attending Eye OPD of a tertiary care eye centre. A sample size of more than 30 was taken in each arm. Consecutive patients attending the Eye OPD were screened for AMD based on visual acuity, the fundus findings and optical coherence tomography consisting of,

a. Non-neovascular AMD: characterized by the presence of drusens, focal hyperpigmentation or hypopigmentation of the RPE or geographic atrophy.
b. Neovascular AMD: characterized by the presence of CNV and associated manifestations such as retinal pigment epithelial detachment, retinal pigment epithelial tears, fibrovascular disciform scarring, and subretinal haemorrhage.

The screened patients underwent detailed ocular examination including best corrected visual acuity, slit lamp biomicroscopy, dilated fundus examination, fundus fluorescein angiography (FFA) & optical coherence tomography (OCT). The patients also underwent systemic evaluation in the form of blood pressure recording, blood sugar fasting and post prandial, lipid profile and ECG. The study population in both DS1 & DS2 comprised of three groups.

Group A: Neovascular AMD.
Group B: Non-neovascular AMD.
Group C: Comprised of age and sex matched controls.

Plasma homocysteine levels were then estimated in all these patients. A three ml venous blood sample was obtained from each participant after an 8-hour fasting. The blood was sent for homocysteine analysis by enzyme immunoassay. The test was done using the Axis Homocysteine Enzyme Immunoassay test for both DS1 & DS2. The normal range of fasting plasma homocysteine was taken as 5-15 micro mol/litre. As the main outcome measure, hyperhomocysteinemia was defined as a plasma homocysteine level of 15 micromol/litre (umol/l) or more.

The results of the three groups in both the subsets were collated, tabulated and analysed using analysis of variance (ANOVA) on logarithmically transformed homocysteine level. The study was conducted in accordance with the Declarations of Helsinki and adheres to tenets of Institutional research guidelines. Informed consent was obtained from all the patients.

RESULTS

A total of 96 patients in each, DS1 & DS2 were included in this study. In DS1, in Neovascular AMD group age ranged between 48 to 80 years, with a mean of 64.68 yrs. In the Non Neovascular AMD group age ranged between 52 to 76 years, with a mean of 64.12 yrs and between 52 to 85 years, with a mean of 65.4 yrs in the controls. Out of the total of 32 patients, there were 19 male & 13 female in Neovascular AMD group, 21 male & 11 female in Non Neovascular AMD group, and 18 male & 14 female in control group (Table 1).

In DS2, in Neovascular AMD group age ranged between 52 to 82 years, with a mean of 65.42 yrs. In the Non Neovascular AMD group age ranged between 50 to 80 years, with a mean of 63.32 yrs and between 48 to 80 years, with a mean of 64.30 yrs in the controls. Out of the total of 32 patients, there were 18 male & 14 female in Neovascular AMD group, 17 male & 15 female in Non Neovascular AMD group, and 20 male & 12 female in control group (Table 1).

In DS1, homocysteine values in the Neovascular AMD group ranged from 03-53 micromol/litres, with a mean of 17.94 micromol/l. Homocysteine values in the Non Neovascular AMD group ranged from 05-23 micromol/litres, with a mean of 11.66 micromol/l. Homocysteine values in the control group ranged from 03-23 micromol/litres, with a mean of 10.97 micromol/l (Table 2).

In DS2, homocysteine values in the Neovascular AMD group ranged from 04-45 micromol/litres, with a mean of 18.03 micromol/l. Homocysteine values in the Non Neovascular AMD group ranged from 04-24 micromol/litres, with a mean of 11.53 micromol/l. Homocysteine values in the control group ranged from 03-21 micromol/litres, with a mean of 10.88 micromol/l (Table 2).

In DS 1, hyperhomocysteinemia was seen in 19 patients (59%) in the Neovascular AMD, 06 patients (19%) in non Neovascular AMD & 04 patients (13%) in control group. In DS 2, hyperhomocysteinemia was seen 19 patients (59%), 7 patients (22%) & 6 patients (19%) in Neovascular AMD, Non Neovascular AMD & control group respectively.

In DS1, amongst overall AMD patients (both non-neovascular and neovascular AMD) 25 patients had raised homocysteine (39%), whereas only 04 patients in the control (13%) had hyperhomocysteinemia.

In DS1, mean homocysteine in the AMD group (both

	DS1			DS2		
	NVAMD	Non NVAMD	Control	NVAMD	Non NVAMD	Control
Age	64.68	64.12	65.4	65.42	63.32	64.3
Male:Female	19:13	21:11	18:14	18:14	17:15	20:12
Percentage of Hypertensives	44%	47%	41%	41%	44%	36%
Percentage of Diabetics	35%	38%	38%	41%	38%	44%

Table-1: Demographic characteristics of the groups included in the study.

	DS1			**DS2**		
	NVAMD	**Non NVAMD**	**Control**	**NVAMD**	**Non NVAMD**	**Control**
Mean Homocysteine value (µmol/l)	17.94	11.66	10.97	18.03	11.53	10.88
Standard Deviation	8.84	4.7	4.63	8.72	5.09	4.33
Range (µmol/l)	03-53	05-23	03-23	04-45	04-24	03-21
No of patients with Hyperhomocysteinemia	19	6	4	19	7	6

Table-2: Serum Homocysteine levels of the groups included in the study. The NVAMD group shows significantly raised levels in both DS1 & DS2.

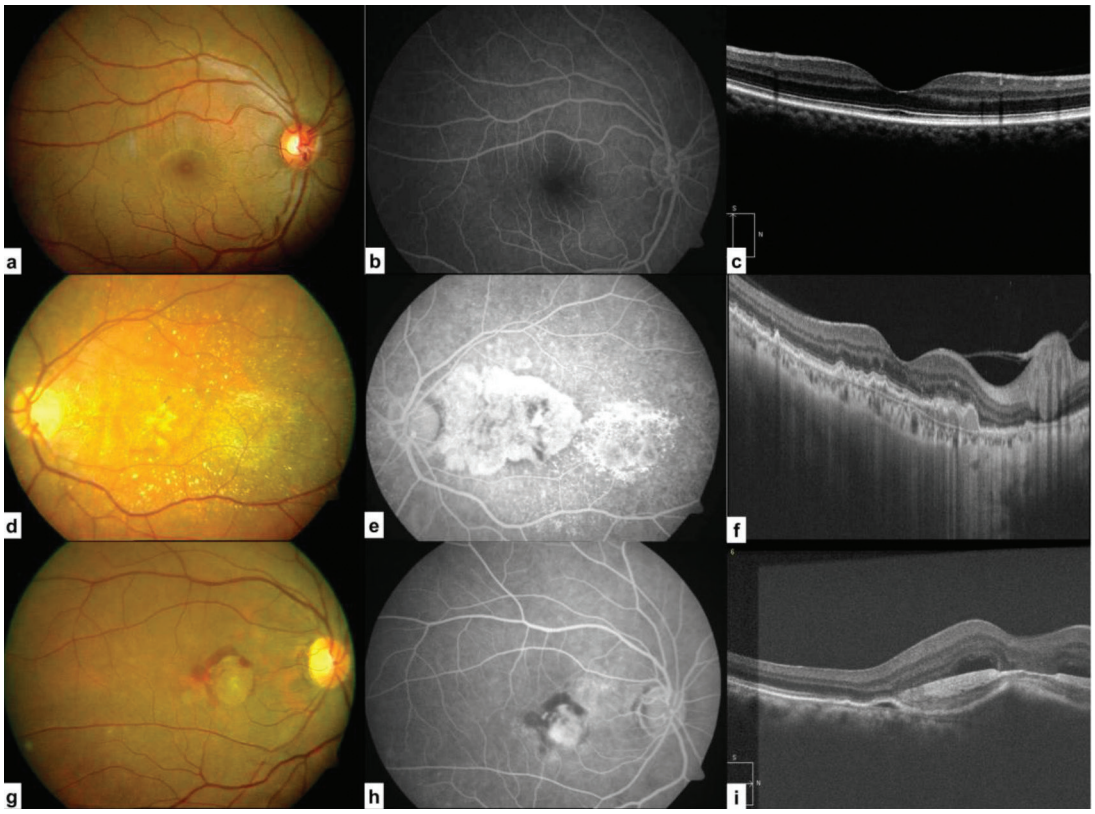

Figure-1: Normal fundus appearance with FFA & OCT of normal fundus (a, b & c). The middle row shows fundus of Non Neovascular AMD with geographic atrophy and its corresponding FFA and OCT (d, e & f). The bottom row shows Neovascular AMD with the characteristic exudative haemorrhagic lesion (g), FFA of Neovascular AMD showing lacy hyperfluorescence (h) & OCT showing Neovascular Choriocapillaries complex (i)

non-neovascular and neovascular AMD) was 14.80 micromol/l whereas it was 10.97 micromol/l in the control group.

In DS 2, Amongst all AMD patients (both non-neovascular and neovascular AMD) overall 26 patients had raised homocysteine (41%), whereas only 06 patients in the control (19%) had hyperhomocysteinemia.

In DS2, mean homocysteine in the AMD group (both non-neovascular and neovascular AMD) was 14.78 micromol/l whereas it was 10.88 micromol/l in the control group.

DISCUSSION

Homocysteine is pivotal to Methionine metabolism which is vital to the physiological functioning of a cell.[7] The role of increased homocysteine in inducing genetic modifications[18], increasing oxidative stress[9] and consequent cell injury is well understood. The effects range from atherosclerosis inducing cognitive damage[20] to retinal diseases.[21] The significance of studying hyperhomocysteinemia lies in a potential therapeutic target[7,14], which is extremely cost effective for population strategies in tackling the visual morbidity of

AMD.[22]

In both DS1 & DS2, in all three groups no statistically significant difference was seen in age and sex distribution.

In DS1, mean homocysteine levels in Neovascular AMD patients was 17.94 micromol/l (range 03-53 micromol/litres) which was significantly higher than the Non Neovascular AMD group which was 11.66 micromol/l (range 05-23 micromol/litres) and in the control group which was 10.97 micromol/l(range 03-23 micromol/litres). In DS2, mean homocysteine levels in Neovascular AMD patients was 18.03 micromol/l (range 04-45 micromol/litres) which was significantly higher than the Non Neovascular AMD group which was 11.53 micromol/l (range 04-24 micromol/litres) and in the control group which was 10.88 micromol/l(range 03-21 micromol/litres).

In both sets of patients, mean plasma homocysteine value in the Neovascular AMD group was statistically significantly higher when compared to the values in the other two groups ($p< 0.05$). In a study done by Axer-Siegel R et al[23] & Nowak M et al[24] mean homocysteine value in Neovascular AMD group was significantly higher than Non Neovascular AMD and control group.

In DS1, mean homocysteine in the AMD group (both non-neovascular and neovascular AMD) was 14.8 micromol/l whereas it was 10.97 micromol/l in the control group. In DS2, the mean homocysteine in the AMD group (both non-neovascular and Neovascular AMD together) was 14.78 micromol/l whereas it was 10.88 micromol/l in the control group. This is in consonance with the study by Kamburoglu et al[11], Rochtchina et al[12], Seddon et al[25], Coral et al[10] and Vine et al[26] which found that patients with both neovascular and non-neovascular types of AMD had significantly higher plasma homocysteine levels compared with the controls. They concluded that an association between elevated plasma homocysteine and AMD regardless of the subtype exists. Javadzadeh et al[27,28] commented on the increased oxidative stress caused by hyperhomocysteinemia and the consequent pathway of neovascular AMD occurrence. This cause and effect relationship was further investigated over the past decade by Gopinath et al[14], Keles et al[29], Huang et al[15] and Bharathselvi et al[30] who reached similar conclusions.

However, these findings have been challenged by few authors. Christen et al in a large population cohort did not find an association between homocysteine and AMD in women[31] or men.[32] However, this study looked at both the neovascular and non-neovascular AMD as a combined group and probably missed the association of hyperhomocysteinemia with NVAMD. Pinna et al did not find an association between hyperhomocysteinemia and NVAMD.[33] A meta-analysis by Pinna et al recommended further studies of cohort designs to establish this association.[34]

The research into the pathogenetic mechanism of hyperhomocysteinemia induced NVAMD included invitro experiments on ARPE cells[16], The effect on blood retinal barrier due to retinal pigment epithelial damage was demonstrated by Mohamed et al[9] Elsherbiny et al[20] and Tawfik et al.[21] Further, in the past two years the role of epigenetic modification induced by hyperhomocysteinemia[18,35] and increased oxidative stress in AMD[36] has been published.

The above findings prompted the authors to research the association of hyperhomocysteinemia and NVAMD in Indian population. Our study is unique in presenting two independent data sets of NVAMD patients with an intervening period of ten years. This helps in filling the knowledge gap in terms of a change in homocysteine levels ascribed to change in the dietary habits or changed environmental conditions in India.

CONCLUSION

In our study mean plasma homocysteine value in the Neovascular AMD group was higher and statistically significant when compared to the values in the other two groups in both DS1 & DS2. In Neovascular AMD group, 59% patients in both DS 1 & DS 2 set had raised homocysteine whereas in Non Neovascular AMD raised homocysteine was seen in 19% and 22% only. By this study, it can be concluded that there exists an association between an elevated plasma level of homocysteine and neovascular AMD, but not with non-neovascular AMD. It can also be concluded that hyperhomocysteinemia is perhaps an independent risk factor for neovascular AMD, however a drawback of our study is the smaller sample size. Based on this study it would appear that the patients with raised homocysteine values should be given Folic Acid, vitamin B6 and B12 supplements.

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