Serum homocysteine levels in patients with retinal vein occlusion

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Abstract

Purpose: To find out role of high serum homocysteine levels in retinal vein occlusion patients at Dr. D.Y. Patil medical College.
Design: A matched case control type of study was conducted from 2016 to 2018.
Materials and Methods: Total serum homocysteine (tHcy) was measured in patients coming at Dr. D.Y. Patil medical college, aged 20 years and above. We evaluated the presence of high homocysteine levels in patients with retinal vein occlusion. We evaluated serum homocysteine levels in 50 patients with retinal vein occlusion coming to our clinic. Control subjects consisted of age and sex matched patients that were referred to our clinic for retinal disease other than vascular occlusion. homocysteine levels between 4 µmol/L to 15 µmol/L were considered normal. High homocysteine level was defined as a total serum homocysteine level above 15 µmol/L.
Results: The mean serum homocysteine level were 13.80+/-8.08 µmol/L (range, 4–33 µmol/L) for cases, and 6.43+/-1.38 µmol/L (range, 4–10 µmol/L) for controls. The mean serum homocysteine levels in cases were more than double that of controls. This difference was very highly statistically significant. Out of the 50 patients with retinal vein occlusion, 13 (26.00%) patients had serum homocysteine levels above normal levels as compared to the controls where none out of the 50 patients had homocysteine levels above normal. (Chi square = 14.94, d.f.=1, p<0.001), This difference was very highly statistically significant. 38 (60%) patients were present with hypertension in both cases and control groups.
Conclusion: High homocysteine levels is a statistically significant risk factor for retinal vein occlusion and it should be evaluated in every patient with retinal vein occlusion.

Keywords: Hyperhomocysteinemia, Retinal vein occlusion.

Introduction

Hyperhomocystienemia is considered as increase of the homocysteine level in blood, serum or plasma. Homocysteine levels in serum between 4 to 15 micromoles/liter (µmol/L) is considered normal. Levels above 15 µmol/L is considered high. Homocysteine levels on an average are below 10 µmol/L. Hyperhomocysteinemia can be moderate type, intermediate type, and severe type depending on the level of serum homocysteine: Moderate (15 to 30 µmol/L), Intermediate (30 to 100 µmol/L), Severe (greater than 100 µmol/L).[1]

Causes of high serum homocysteine levels can be genetic factors determinants, lifestyle (vegetarian diet, high coffee consumption), medicines (methotrexate), etc.[2-5] Inadequate levels folate or of the B vitamins account for very high number of cases of hyperhomocysteinemia.[6] McCully and Wilson proposed the theory of high serum homocysteine levels leading to arteriosclerosis.[7] Research relating high homocysteine levels with vascular disorders has been done extensively in the last 10 to 15 years.[8,9] Increase in serum homocysteine level has been associated with myocardial infarction, stroke and carotid wall thickening in adults with no history of atherosclerotic disease. Various European studies has shown that high homocysteine levels are an independent risk factor for vascular disease.[9] High serum homocysteine level is a high risk factor for venous thrombosis, has been shown by many studies.[10,11] A large multicentre study (The eye disease case control study group), have suggested that cardiovascular risk factors are also the risk factors for retinal vein occlusions.[12] But they did not include measurement of serum homocysteine levels in their study. Our study seeks to determine whether high serum homocysteine levels is a risk factor for retinal vein occlusion. Limited studies on this issue are available in the India. Our study estimated the role of high serum homocysteine levels in the occurrence of retinal vein occlusion.

Materials and Methods

Our study was conducted between 2016 and 2018. We took a verbal consent of the patients. The study type was a matched pair case control study. The difference in the mean levels of serum homocysteine among cases group and controls group was around 14 µmol/L and this was used to calculate the sample size. The standard deviation in cases group as high as 26 µmol/L and in control group as high as 10 µmol/L was considered. We selected 50 patients with Retinal Vein Occlusion and 50 cases without Retinal vein occlusion. This gave an 80% precision to our study. We considered 1:1 ratio of age and sex matched cases and controls. Patients aged 20 years and older, diagnosed at our clinic between 2016 and 2018, and having Retinal vein occlusion in were included in cases group. Age- and sex matched patients with retinal disease without Retinal Vein Occlusion were included in the controls group. Diabetics, hyperthyroidism, patients having tobacco or tobacco related products, patients consuming alcohol, patients having undergone eye surgery in the last 1 year, pregnant women, were excluded from the study. Senior ophthalmologist and ophthalmology residents undergoing training in ophthalmology were our field staff. Visual acuity for distance, and best corrected visual acuity was noted using Snellen's literate chart. Visual acuity was checked using the finger counting method if the vision was less than 6<60.

The intra ocular pressure was measured with applanation tonometer (Appasamy Associates, Chennai, India). Anterior segment was assessed using a slit lamp (Appasamy Associates, Chennai, India). The posterior segment was examined with indirect ophthalmoscope (Appasamy Associates, Chennai, India) and + 20 D Volk lens. Slit lamp biomicroscopy with +78 D volk lens was also used for diagnosis. Fluorescein angiography and Optical Coherent Tomography (OCT) was done to confirm the diagnosis. We also classified the retinal vein occlusion into central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). A fasting blood sample and urine sample were collected and assessed in the laboratory to calculate homocysteine levels. High performance liquid chromatography with electrochemical detection was used. Homocysteine level of 15 µmol/L or less was considered as normal. Levels above 15 µmol/L were considered as high. A manual mercury sphygmomano meter was used to measure systolic and diastolic blood pressures. Patients on antihypertensive medication and patient with a systolic pressure of more than 140 mmHg and diastolic pressure more than 90 mmHg were considered as hypertensive patients. These patients were examined by the physicians in medicine department. They were further evaluated for cardiovascular pathologies and treated accordingly. Microsoft XL spreadsheets was used for data entry. We took the help of our statisticians in preventive and social medicine department to do the statistical analysis. Since the data was not normally distributed as indicated by Shapiro-Wilk test, Non parametric test i.e. Mann Whitney test was used to compare the homocysteine levels in cases and controls. To compare the homocysteine levels above normal (>15 µmol/L) in cases and controls and to calculate the p value, Chi square test was used. Patients with Retnal vein occlusion was then treated with different modalities like anti VEGF injections and laser photocoagulation as per the indication.

Results

We tested serum homocysteine levels in 50 patients with retinal vein occlusion and 50 patients with retinal diseases without retinal vein occlusion. Table 1 shows the characteristics of cases and control group patients. The mean serum homocysteine level was 13.80+/-8.08 µmol/L (range, 4–33 µmol/L) in the cases group, and 6.43+/-1.38 µmol/L (range, 4–10 µmol/L) for control group. The mean serum homocysteine levels in cases group were more than double that of controls. This difference was very highly statistically significant. Table 2 shows the serum homocysteine levels of patients in cases and control group. Serum homocysteine levels above 15 µmol/L was considered as hyperhomocysteinemia. 13 (26.00%) out of the 50 patients with retinal vein occlusion had hyperhomocysteinemia as compared to the control group where none of the 50 patients had homocysteine levels above normal. (Chi square = 14.94, d.f.=1, p<0.001). This difference was very highly statistically significant. Table 3 shows high serum homocysteine levels between cases and controls groups. Eighteen patients (36%) of the 50 cases had a central retinal vein occlusion and Thirty-two (64%) of the 50 patients had branch retinal vein occlusions. High serum homocysteine levels in different types of retinal vein occlusions were also compared (Table 4), but statistically significant correlation could not be found.

In patients with retinal vein occlusion 38 were hypertensives while 12 patients had normal systolic and diastolic pressures. In control group also, 38 patients were hypertensives and 12 had normal blood pressure.

The 50 patients with retinal vein occlusion were divided into three categories depending on their best corrected vision: 31 eyes had moderate visual loss (Vision 6/18 to 6/60) out of which 1 eye had Central retinal vein occlusion and 30 eyes had Branch retinal vein occlusion. Severe vision loss (Vision <6/60 but ≥3/60) was seen in 6 eyes out of which 4 eyes had Central retinal vein occlusion and 2 eyes had Branch retinal vein occlusion. Very severe vision loss (Vision<3/60) was seen in 13 eyes out of which all 13 cases were of Central retinal vein occlusion and none was of Branch retinal vein occlusion. Table 5 shows best corrected vision in eyes with different types of retinal vein occlusion. For each of these categories, the percentage of eyes from patients with high serum homocysteine levels (>15 µmol/L) was 16%, 3%, and 4%, respectively. It appears that vision loss is less in patients with branch retinal vein occlusion as compared to central retinal vein occlusion.

Table 1: Baseline data of cases and controls

	Cases	Control
Gender (Male)	40(80%)	40(80%)
Hypertension	30(60%)	30(60%)
Age {Mean(SD)}	60.22(15.52)	62.52(13.35)

Table 2: Homocysteine levels in cases and controls

	N	Mean	SD	Median	Mann Whitney U	P
Controls	50	6.43	1.38	6.35	381	<0.001
Cases	50	13.80	8.08	11.7		

Table 3: Hyperhomocysteinemia between cases and controls

Homocysteine category	Control	Cases
	No.(%)	No.(%)
Normal	50(100)	37(74)
Raised	0(0)	13(26)
Total	50(100	50(100)

Chi square = 14.94, d.f.=1, p<0.001

Table 4: Hyperhomocysteinemia and type of retinal vein occlusion

Grades of serum homocysteinemia	Range (µmol/L)	Persons with CRVO	Persons with BRVO	No occlusion
Normal	4–15	0	0	50
Moderate	16–30	5	6	0
Intermediate	31–100	1	1	0
Severe	> 100	0	0	0

Table 5: Best corrected vision in eyes in different types of retinal vein occlusion

Type	No visual impairment	Moderate Vision loss (Vn 6/18 to 6/60)	Severe Vision loss(Vn <6/60 but ≥3/60)	Very severe vision loss (Vn<3/60)
Central retinal vein Occlusion	0	1	4	13
Branch retinal vein occlusion	0	30	2	0

Discussion

The result in our studies clearly show that a statistically significant association exist between high serum homocysteine levels and retinal vein occlusion. It is also seen that although high homocysteine levels are risk for retinal vein occlusion, the levels of homocysteine had no relation with the type of retinal vein occlusion. Other studies in literature also showed similar association and our findings matched with the findings of other studies.[24,25,27]

The results did not show hypertension as the cause of high serum homocysteine levels. Hypertension leads to atherosclerotic changes in blood vessels and is associated with the age of patients.[17]

The results show that patients with central retinal vein occlusion showed poor vision as compared to branch retinal vein occlusion but it had no statistically significant association with the level of hyperhomocysteinemia.[29]

Other researchers have documented poor vision in patients with vein occlusion.[27,28,30] Our study also had similar results.

A large multicentre eye study, had suggested cardiovascular screening in patients with retinal vein occlusion but our study suggests that an additional screening for hyperhomocysteinemia should also be done in patients with retinal vein occlusion.[12] High homocysteine levels can easily be treated with inexpensive vitamin preparations containing folic acid and B12 and is completely reversible.[13,14] High homocysteine levels can lead to atherosclrosis and venous thrombosis also.[8-11] Since high homocysteine levels affect both arteries and veins, the risk of occlusion may significantly increase especially at the sites of A-V crossings and where arteries and veins have common adventitia.[15] This may hence be one of the risk factors in pathogenesis of retinal vein occlusion.[16] In our study none of the patients with retinal vein occlusion had been previously tested for serum homocysteine levels. Systemic hypertension was equally common in cases and control groups (60% vs 60%) like in other case-control studies.[12] The mean age showed a difference of 2 years between controls and cases with controls 2 years younger than the cases group. Both cases group and control group had equal percentage of men and women with more men than women in each group. (80% vs 80%)[18] overall, the control group appears comparable to the group with retinal vein occlusion in major characteristics.

Homocysteine metabolism can be affected by genetic enzyme defects or deficiency of vitamins B12 and folic acid that are needed as precursors of these enzymes[26] Hyperhomocysteinemia can occur due to various other causes, including lifestyle determinants (such as coffee consumption, vegetarian diet), serum vitamin status, and genetic composition.[3,6,19] The framingham study suggests low plasma folic acid levels as the cause for high homocysteine levels in blood in elderly patients.[6] Various studies have shown a higher risk of vascular disease in patients with folate, vitamin B6 and vitamin B12 deficiency.[20,21]

Numerous studies have shown and suggested that a dietary folic acid supplement should be recommended now to increase plasma folate levels and reduce plasma homocysteine levels to decrease the risk of vascular episode.[13,20,22] Various studies have suggested that it is advisable to bring serum homocysteine levels below 10 µmol/L, in order to avoid atherosclerotic changes in vessel wall.[22] Various researchers have recommend that everyone should consume 400 mg of folic acid per day as a vitamin supplement.[22,23] In our study 29 (58%) had total plasma homocysteine levels above 10 µmol/L. Thus while investigating patients with retinal vein occlusion, serum homocysteine levels should be evaluated.[31,32]

One of limitations in the study was in the calculation of sample size. As it was based on the assumption of difference of 15 µmol/L, this could be argued to be too high, resulting in reduced precision within the study.

Conclusion

In conclusion, retinal vein occlusion can be associated with atherosclerosis, and other cardiovascular risk factors. These factors should be controlled, according to the current guidelines, to avoid relapses. Our study suggest that serum homocysteine should also be measured in all patients with retinal vein occlusion, in order to treat hyperhomocysteinemia with vitamin B12 and folate supplementation. Nevertheless, further prospective and

controlled trials, with strong cardiovascular end-points, are needed to ascertain the usefulness of this therapeutic approach in these patients.

Conflict of Interest: None.

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