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Plasmahomocysteine Levels in Retinal Vascular Occlusive Disease

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Abstract: ***Background: A moderately elevated plasma concentration of the sulphur amino acid homocysteine is an independent risk factor for atherosclerotic vascular disease. This study was done to assess the relationship between retinal vascular occlusive disease and total plasmahomocysteine level (tHcy). Methods: A prospective case - control study involving hospital based controls and cases with retinal artery occlusion, centralretinal vein occlusion (including hemiretinal vein occlusion), and branch retinal vein occlusion was performed. The relation between elevated plasma homocysteine level (tHcy), defined as a level greater than or equal to 12 µmol/l and risk of retinal vascular occlusive disease was examined. Results: 87 cases of retinal vascular occlusive disease were considered. This included 26 cases of retinal artery occlusion, 40cases with central retinal vein occlusion, and 21 cases of branchretinal vein occlusion. The cases were compared with 87 age matched controls. Mean tHcy levels were higher in all disease groups and this difference was significant in patients with retinal artery occlusions (p= 0.032) and patients with central retinal vein occlusion (p=0.0001). When adjusted for known cardiovascular risk factors, tHcy was an independent risk factor for retinal vascular occlusive disease (OR2.85 (95%CI1.43–5.68)). Conclusions: Elevated total plasma homocysteine level (tHcy) is an independent risk factor for retinal vascular occlusive disease.***

1. Introduction

Homocystinuria was first described among subjects with mental retardation, ocular and skeletal abnormalities, and a high risk of thromboembolism[1]. In such individuals whose plasma total homocysteine (tHcy) concentrations are highly elevated (often in excess of 100 µmol/l), the underlying defect is usually one of inherited dysfunction of the enzyme cystathionine B - synthase (CBS) [2]. The observation of atherosclerotic - like lesions in two neonates with homocystinuria, one with CBS deficiency and one with a defect in cobalamin metabolism, led to the proposal that homocysteine is a causative factor for atherosclerotic vasculardisease[3]. This hypothesis has been supported by evidence from many studies demonstrating a significant relation between elevated tHcy concentrations and risk of venous thrombosis, coronary, cerebral, and peripheral vascular disease[4–8]. Certain nutritional deficiencies are common determinants of elevated tHcy concentration[9]. Plasma concentrations and dietary intake of folate, vitamin B6, and B12 relate inversely to the tHcy level[9]. Supplementation with such vitamins lowers tHcy levels and may reduce vascular disease risk[8–10]. The present study was undertaken to assess the relation between retinal vascular occlusive disease and moderately elevated fasting levels of tHcy.

2. Materials and Methods

Cases:
Cases were taken from the routine Out Patient Department, Department Of Ophthalmology, Government Medical College, Anantnag, Jammu and Kashmir, India. 87 cases with clinical and investigational evidence of retinal vascular occlusive disease were studied including 40 cases of central and hemiretinal vein occlusion (which were considered together), 21casesof branch retinal vein occlusion, and 26 cases of retinal artery occlusion (central and branch were included together). Exclusion criteria were recent major systemic illness (including myocardial infarction), evidence of vasculitis, renal, hepatic, or thyroid disease, cardiomyopathy, pregnancy, psychiatric illness, chronic alcohol abuse, anticonvulsant therapy, and recent (within3 months) exposure to nitrous oxide.

Controls
87 hospital based controls were age matched and had no history orclinical evidence of retinal vascular disease. The majority of controls were patients attending for routine cataract extraction (n=59) while other controls had a range of surgical procedures including trabeculectomy (n=15), ptosis repair (n=4), squint repair (n=2), glaucoma drainage device implant (n=1), and excision of pterygium (n=6). Exclusion criteria were abs in the case group.

Variables Examined:
Based on a standardised format, demographic, cardiovascular risk factors, and diagnostic data were recorded for each subject. Diagnostic data consisted of biochemical, haematological, and endocrine variables that are known to alter tHcy levels. All blood samples were taken fasting (samples were taken preoperatively in controls requiring surgical treatment) and analysed using standard automated laboratory techniques. Blood samples for tHcy were immediately placed on ice, centrifuged at 4°C and 3500 rpm for 6minutes within 1 hour and the resultant plasma supernatant was aspirated, frozen, and stored at −70°C. tHcy was determined by high performance liquid chromatography and fluorescence detection[11].

Statistical Analysis:
All of the controls were compared with cases in each of four categories including all cases of retinal artery occlusions, all cases of retinal vein occlusions, cases of central retinal vein occlusions (including hemiretinal vein occlusions), and cases of branch retinal vein occlusions. An elevated tHcy level was defined as greater than or equal to 12 µmol/l. Logarithmic transformations and geometric means were used for variables showing a marked positive skew.

Univariate analysis was carried out initially to determine the significance of associations between the controls and each of the four groups of patients with regard to the previously outlined variables using the Student's t test for normally

distributed continuous variables, the Mann–Whitney U test for continuous variables with a skewed distribution, and the $\chi 2$ test for categorical variables. Single logistic regression models were used to examine the relation between elevated tHcy and known risk factors including hypertension and glaucoma in venous occlusive disease and hypertension and previous carotid surgery in arterial occlusive disease.

3. Results

Age, Sex, and Retinal Vascular Occlusive Disease

26 cases of retinal artery occlusion and 61 cases of retinal vein occlusion were compared with 87 controls.48% of the study participants were male (n=84) and while there were similar proportions of males to females in the control and venous occlusion groups there was a significantly higher proportion of males with retinal artery occlusions (p=0.009) (Table1)

Age, sex, and blood levels of tHcy, total cholesterol, and creatininein controls and cases

	Controls	All	Arterial	Vein	Centralvein	Branchvein
No. of subjects	87	87	26	61	40	21
Mean age (years)	70.2	68.5	66.8	69.2	70.2	67.2
Sex, % male	41.2	55.2	73	47.5	50	42.8
p Value		0.095	0.009	0.565	0.473	0.901
GM fasting tHcy (µmol/l)	10.7	12.9	12.9	13.0	13.7	11.7
p Value		<0.0001	0.032	<0.0001	0.0001	0.097
GM serum creatinine (µmol/l)	92	95	99	93	96	87
p Value		0.723	0.405	0.989	0.640	0.466
GM fasting total cholesterol (µmol/l)	5.8	5.6	5.7	5.6	5.5	5.8
p Value		0.783	0.453	0.431	0.284	0.957

Risk factors for cardiovascular and retinal vascular occlusive disease

No significant difference was noted between cases and controls in the mean serum total cholesterol levels, use of lipid lowering agents, prevalence of diabetes, ischaemic heart disease, previous transient ischaemic attack, or stroke (Table 2). A significantly higher proportion of cases of retinal artery occlusion had a history of carotid surgery than controls (p=0.0004). In addition, a higher proportion of cases in all groups except controls were on treatment for hypertension, although this difference was only significant in cases of retinal artery occlusion (p=0.007) and all cases of retinal vein occlusion taken together (p = 0.037) (Table 2). A smaller proportion of cases than controls were smokers. A significantly higher proportion of cases of central retinal vein occlusion than controls had glaucoma (p=0.046).

Table 2

	Controls	All	Arterial	Vein	Centralvein	Branchvein
No of subjects	87	87	26	61	40	21
Lipid lowering therapy (%)	4.6	6.9	1.5	4.9	7.5	0.0
p Value		0.744	0.197	1.00	0.677	1.00
Treatment for hypertension (%)	36.8	58.6	69.2	54.1	52.5	57.1
p Value		0.006	0.007	0.037	0.140	0.145
Current smokers (%)	32.2	17.2	19.2	16.4	15.0	19.0
p Value		0.035	0.303	0.048	0.069	0.359
Diabetes mellitus (%)	8.0	11.5	15.4	9.8	5.0	19.0
p Value		0.669	0.273	0.933	0.718	0.218
Ischaemic heart disease (%)	16.1	23.0	27.0	21.3	27.5	9.5
p Value		0.339	0.252	0.553	0.207	0.732
Previous carotid endarterectomy (%)	0.0	6.9	19.2	1.6	0.0	4.7
P Value		0.028	0.0004	0.416	1.00	0.201
Previous TIA/CVA (%)	4.6	12.6	15.4	11.5	12.5	9.5
p Value		0.105	0.080	0.201	0.138	0.330
Treatment for glaucoma (%)	10.0	17.0	4.0	23.0	22.5	19.0
pValue		0.11	0.411	0.020	0.046	0.13

Total plasma homocysteine level as a risk factor for retinal vascular occlusive disease

When compared with the control group, mean tHcy levels were higher in all the disease groups and this difference was significant in all groups except cases of branch retinal vein occlusion (p =0.097) (Table 1). On univariate analysis, elevated tHcy conferred a significantly increased risk of retinal vascular occlusive disease (arterial and venous disease combined; OR (95%CI): 2.89 (1.52–5.50)) which remained significant following adjustment for the conventional risk factors of glaucoma, hypertension, and diabetes (OR 2.85 (95% CI 1.43–5.68)) (Table 3). However, when retinal artery occlusive disease was considered alone, elevated tHcy was a significant risk factor only on univariate analysis (OR 2.53 (95%CI 1.02–6.29)). While elevated tHcy was a significant risk factor for all vein occlusions combined on both univariate and multivariate analysis, this was not the case when branch vein occlusions were considered alone (Table3).

	Univariate		Multivariate adjusted	
Versus 87 controls	Odds Ratio	95%CI	Odds Ratio	95%CI
All cases (n=87)	2.89	1.52–5.50	2.85	1.43–5.68
Arterial (n=26)	2.53	1.02–6.29	2.02	0.76–5.33
Allvein (n=61)	3.05	1.52–6.13	3.33	1.56–7.14
Central vein (n=40)	4.00	1.81–8.82	4.01	1.70–9.48
Branch vein (n=21)	1.82	0.66–4.97	1.87	0.64–5.42

4. Discussion

Elevated tHcy is an independent risk factor for atherosclerotic vascular disease and interacts with other risk factors such as smoking and hypertension to increase cardiovascular disease risk[7–8]. tHcy 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[6].

Information relating abnormalities of homocysteine metabolism to retinal vascular occlusive disease are sparse and confined to two case reports and one small, uncontrolled series[12–14]. The finding that elevated tHcy is an independent risk factor for central retinal vein occlusion is consistent with earlier findings implicating elevated tHcy in thrombus formation[4–7]. Furthermore, thrombus formation from rheological abnormalities other than elevated tHcy has been implicated in previous studies as a possible aetiological factor in central and hemiretinal vein occlusions[17]. However, while central retinal vein occlusions are associated with similar risk factors to retinal arterial occlusive disease, local factors such as atherosclerotic retinal arteries compressing retinal veins atarteriovenous crossings may be more important in the aetiology of branch retinal vein occlusions[17]. This could explain the difference in risk associated with elevated tHcy between central and branch retinal vein occlusions found in this study.

While tHcy levels were significantly higher in cases of retinal artery occlusion, the small number of patients with retinal artery occlusion included in this study precludes an examination of the relation between elevated tHcy, retinal artery occlusion, and two previously determined risk factors, carotid atheroma andhypertension[16–18]. Contrary to expectations, a lower proportion of cases than controls were smokers. It is more likely that smokers had ceased at the time of their retinal event, or that they were under represented in this elderly population because of premature mortality, than that smoking protects against retinal vascular disease.

Recent reports indicate that both nutritional and genetic factors are important determinants of elevated tHcy levels and that dietary supplementation with folic acid can reduce tHcy[8–10]. The clinical inference is that measurement, treatment, and monitoring of tHcy levels may be valuable in the management of patients with retinal vascular occlusive disease not only in young or atypical patients but in those with bilateral involvement, disease in an only eye, or those in whom wide spread cardiovascular disease is suspected.

5. Conclusions

Elevated tHcy is an independent risk factor for retinal vascular occlusive disease. In addition to an evaluation of all conventional cardio vascular risk factors, measurement of tHcy may be important in the initial investigation and management of patients with retinal vascular occlusive disease. Lowering elevated tHcy levels by administration of folic acid could improve prognosis in patients with such disease.

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