Plasma Homocysteine Is Elevated in Patients With Exfoliation Syndrome

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• PURPOSE: To compare plasma homocysteine concentrations among patients with exfoliation syndrome, exfoliative glaucoma, normal-tension glaucoma, and normal control subjects without vascular or inflammatory ocular disease or glaucoma.
• DESIGN: Cross-sectional study.
• METHODS: We tested 25 patients with exfoliation syndrome, 50 with exfoliative glaucoma, 25 with normal-tension glaucoma, and 24 control subjects. Fasting plasma homocysteine concentrations were measured by fluorescence polarization immunoassay. Patients using vitamin supplements or medications known to alter serum homocysteine were excluded.
• RESULTS: Homocysteine levels were higher in both exfoliation groups compared with controls (exfoliation syndrome: $P = .003$; exfoliative glaucoma: $P = .009$); levels in normal-tension glaucoma were higher than but not significantly different from those in controls ($P = .2$). Hyperhomocysteinemia was present in 16 of 25 (64%) exfoliation syndrome patients, 28 of 50 (56%) exfoliative glaucoma patients, 13 of 25 (52%) normal-tension glaucoma patients, and 7 of 24 (29.2%) controls ($P = .005$). Multiple logistic regression analyses comparing exfoliation syndrome and exfoliative glaucoma patients with controls indicated that elevated plasma homocysteine concentration was a significant risk factor for exfoliation syndrome, in both those patients (odds ratios per 1.0 μmol/l increase in plasma homocysteine concentrations = 1.47; 95% confidence interval [CI] = 1.08–2.0) and in exfoliative glaucoma patients (odds ratio = 1.3; 95% CI = 1.07–1.6). Although exfoliative glaucoma and normal-tension glaucoma patients were not signficantly different with respect to hyperhomocysteinemia, logistic regression modeling of exfoliative glaucoma vs normal-tension glaucoma patients showed that an increased homocysteine concentration was a significant risk factor for exfoliation syndrome in the presence of glaucoma (odds ratio per 1.0 μmol/l increase in homocysteine = 1.2, 95% CI = 1.0–1.4). These relationships were not affected by adjustment for potential confounding due to sex, history of hypertension, or other factors.
• CONCLUSIONS: Elevated plasma homocysteine, a risk factor for cardiovascular disease, is more common in exfoliation syndrome and exfoliative glaucoma patients than healthy controls. Patients with exfoliation syndrome may benefit from measurement of homocysteine levels. (Am J Ophthalmol 2003;136:41–46. © 2003 by Elsevier Inc. All rights reserved.)

EXFOLIATION SYNDROME IS AN AGE-RELATED, GENERalized disorder of the extracellular matrix characterized by production and progressive accumulation of a fibrillar material in both various ocular tissues and also in connective tissue portions of various visceral organs.[1] Overall, it is the most common identifiable cause of glaucoma, accounting for the majority of cases in some countries.[2]

Exfoliation syndrome and hyperhomocysteinemia share common associations with various disorders. Mild hyperhomocysteinemia is an independent risk factor for premature vascular disease,[3] myocardial infarction,[4] and stroke.[5] Exfoliation syndrome is correlated positively with a history of hypertension, angina, myocardial infarction, or stroke, suggestive of vascular effects of the disease.[6] Exfoliation syndrome has been found in patients with Alzheimer disease.[7] Significantly elevated homocysteine levels were also found in patients with Alzheimer disease as well as in patients with vascular dementia.[8]

An association of exfoliation syndrome with branch and central retinal vein occlusion has been suggested.[9–11] Similarly, hyperhomocysteinemia has been suggested to be a risk factor for central retinal vein occlusion[12,13] and also

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for nonarteritic anterior ischemic optic neuropathy and central retinal artery occlusion.[14,15]

Although exfoliation syndrome and hyperhomocysteinemia appear to be associated with many common disorders, no study has examined patients with the syndrome for elevated levels of homocysteine. We hypothesized that homocysteine level is elevated in patients with exfoliation syndrome. We evaluated the possibility of a relationship by measuring total plasma homocysteine level in exfoliation syndrome patients with or without glaucoma.

METHODS

CONSECUTIVE PATIENTS WITH UNILATERAL OR BILATERAL exfoliation syndrome with and without glaucoma from The New York Eye and Ear Infirmary and a private clinic between October 2001 and April 2002 were invited to participate. To evaluate whether homocysteine levels of exfoliative glaucoma patients are independent of glaucomatous optic neuropathy, a group of normal-tension glaucoma patients was also included for comparison. This group was chosen to exclude as effectively as possible patients with preclinical exfoliation syndrome, which is uncommon in patients with normal-tension glaucoma. Subjects without ocular disease were included as controls.

Diagnosis of exfoliation syndrome without glaucoma was based on the presence of typical exfoliation material on the anterior lens capsule in one or both eyes with a normal optic disk and visual field and intraocular pressure (IOP) $\leq$ 21 mm Hg in both eyes. The presence of glaucoma was defined by IOP $>$ 21 mm Hg and typical glaucomatous cupping and visual field loss in at least one eye. Patients with exfoliation syndrome and ocular hypertension were excluded.

Normal-tension glaucoma patients were characterized by the presence of glaucomatous optic neuropathy and visual field loss in at least one eye and no recorded IOP $>$ 21 mm Hg. Control subjects had no history of elevated IOP, normal optic disks and visual fields, and no exfoliation material on the anterior lens capsule. In most cases, these were spouses of patients with exfoliation syndrome. There were no significant differences in age or sex between the control group and the other groups.

We excluded patients taking vitamins and medications known to affect homocysteine measurements, such as fibrates, carbamazepine, phenytoin, antifolates (methotrexate and trimethoprim), vitamins B6 and B12, folic acid, or betaine. We excluded diseases known to affect homocysteine levels, such as impaired renal function, cancer, or history of ocular vascular or inflammatory disease, and also patients unwilling or unable to give consent.

The study was approved by the Institutional Review Board of the New York Eye and Ear Infirmary, and informed consent was obtained from all subjects. A detailed medical history was obtained from all patients to determine those with known or suspected diabetes mellitus, systemic hypertension, peripheral or coronary artery disease, venous thrombotic events, cerebrovascular disease, postmenopausal hormone replacement, and other current drug therapy. All patients underwent a complete ophthalmic examination, including visual acuity, external examination, slit-lamp examination, gonioscopy, tonometry, fundoscopy, and visual field examination.

Subjects fulfilling eligibility criteria underwent a fasting blood test for homocysteine. A 2-ml blood sample was immediately centrifuged after clot formation at 3000 *g* for 6 minutes, and plasma was removed within 45 minutes. The specimen was transported on crushed ice to the laboratory of the Pathology Department of the New York Eye and Ear Infirmary, frozen, and analyzed for homocysteine by fluorescein polarization immunoassay within 3 days by Quest Diagnostics. In this study, hyperhomocysteinemia was defined as total plasma homocysteine level above 9 μmol/l. This is the reference used by our laboratory. Patients were informed about their homocysteine plasma levels. Patients with elevated levels were advised to discuss the result with their personal physician for possible treatment.

The χ^2 test and the Fisher exact test (two-tailed) were used to evaluate categorical data. Continuous variables were compared between groups using the nonparametric Kruskall-Wallis test and the Wilcoxon signed-rank test (homocysteine data had a skewed, nonnormal distribution). Logistic regression analysis was used to compute odds ratios and 95% confidence intervals (CI) considering homocysteine levels and potential confounders for entry. Statistical analyses was performed using SAS Release 8.02 (SAS Institute, Cary, North Carolina, USA), and with Egret for Windows, version 2.0.31 (Cytel Statistical Software, Cambridge, Massachusetts, USA). Graphical analysis of data were performed using SPSS for Windows version 11.0 (SPSS, Chicago, Illinois, USA).

RESULTS

A TOTAL OF 124 SUBJECTS PARTICIPATED IN THIS STUDY, including 50 with exfoliative glaucoma, 25 with exfoliation syndrome, 25 with normal-tension glaucoma patients, and 24 control subjects. As shown in Table 1, there were no significant differences between groups in age, sex, systemic hypertension, peripheral or coronary artery disease, diabetes or cerebrovascular disease, or (among women) history of hormone replacement therapy ($P = .9$). There were proportionately more Hispanics among controls than among other patient groups, leading to a near-significant difference in the distribution of race/ethnicity across patients groups ($P = .07$).

Individual plasma homocysteine concentrations and group median values are shown in Figure 1. The nonparametric Kruskal–Wallis test indicated that the median

TABLE 1. Demographic Characteristics by Study Group

	Exfoliation Syndrome (n = 25)	Exfoliative Glaucoma (n = 50)	Normal-tension Glaucoma (n = 25)	Controls (n = 24)	*P* Value
Age (years)					
Range	54–80	50–86	53–88	50–85	
Mean ± SD	71.1 ± 8.1	71.9 ± 8.9	70.3 ± 10.2	69.4 ± 11.9	.75*
Sex					
Male, n (%)	9 (36)	22 (44)	11 (44)	10 (42)	
Female, n (%)	16 (64)	28 (56)	11 (56)	10 (58)	.9†
Race, n (%)					
White	24 (96)	46 (92)	20 (80)	20 (83.3)	.07†
Hispanic	0	4 (8)	4 (16)	4 (16.7)	
Black	1 (4)	0	0	0	
Asian	0	0	1 (4)	0	
Systemic hypertension, n (%)	11 (44)	16 (32)	12 (48)	8 (33.3)	.5†
Peripheral or coronary artery disease, n (%)	7 (28)	12 (24)	5 (20)	6 (25)	.9†
Diabetes, n (%)	1 (4)	3 (6)	2 (8)	3 (12.5)	.7†
Cerebrovascular disease, n (%)	1 (4)	1 (2)	1 (4)	1 (4)	.9†

*P value calculated by Kruskal-Wallis test.
†P value calculated by chi-square or Fisher exact test.

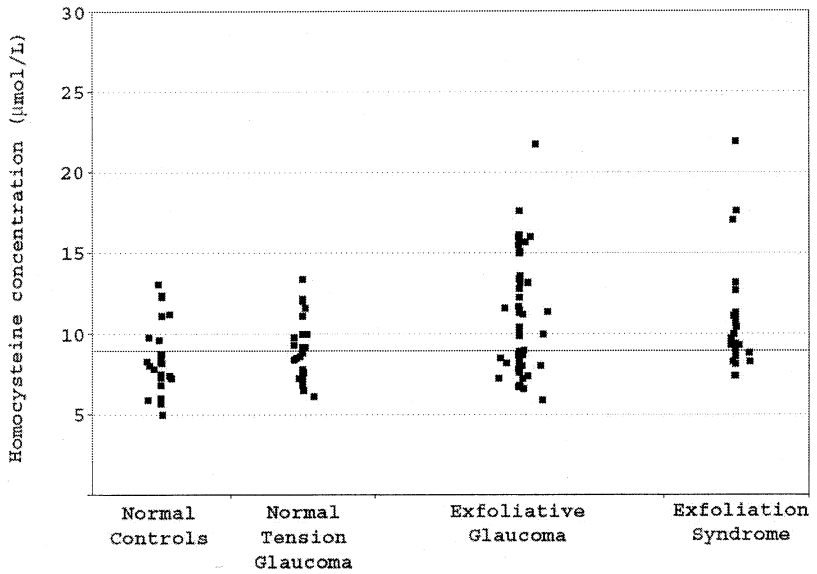

FIGURE 1. Individual homocysteine concentrations (umol/l) in controls (n = 24), patients with exfoliation syndrome without glaucoma (XFS, n = 25), patients with exfoliation syndrome with glaucoma (XFG, n = 50), and patients with normal-tension glaucoma (NTG, n = 25). The solid horizontal line represents the cutoff value (9 µmol/l) for normality.

homocysteine concentrations among the four groups were significantly different ($P = .009$). Median values were 10.0 µmol/l in exfoliation syndrome patients without glaucoma, 10.1 µmol/l in exfoliative glaucoma patients, 9.1 µmol/l in normal-tension glaucoma patients, and 8.3 µmol/l in controls (Table 2). Homocysteine concentrations in patients with normal-tension glaucoma were not significantly different from those in controls ($P = .2$ by the Wilcoxon rank sum) but were higher among exfoliative glaucoma patients and controls ($P = .009$) and also among exfoliation syndrome patients and controls ($P = .003$). Hyperhomocysteinemia was present in 64% (16/25) of exfoliation syndrome patients, 56% (28/50) exfoliative glaucoma patients, 52% (13/25) of normal-tension glaucoma patients, and 29% (7/24) of controls ($P = .005$).

Hyperhomocysteinemia was observed in 71% (37/52) of men compared with 36% (26/72) of women ($P = .0001$). Hypertension also was associated with hyperhomocysteine-

TABLE 2. Median of Plasma Homocysteine Levels and Frequency of Hyperhomocysteinemia

Group	Median (Range) μmol/l	Hyperhomocysteinemia
Exfoliation syndrome	10.0 (7.4–21.9)	64%
Exfoliation glaucoma	10.1 (5.9–21.7)	56%
Normal-tension glaucoma	9.1 (6.1–13.4)	52%
Control	8.3 (5.0–13.1)	29%
P value	.009*	.005†

*Kruskall-Wallis test.
†Chi-square test.

mia with near-significance ($P = .06$). Of 47 patients with a history of hypertension, 29 (61.7%) had hyperhomocysteinemia, compared with 44% of those without a history of hypertension. As neither of these variables differed substantially among patient groups, they did not meet the requirement for confounders, namely that associations exist both with the posited exposure, hyperhomocysteinemia, and with disease.

Multiple logistic regression analyses comparing the various patient groups with the single control group indicated that elevation in plasma homocysteine concentration was a significant risk factor for exfoliation syndrome (odds ratio per 1.0 μmol/l increase in homocysteine concentration = 1.47, 95% CI = 1.08–2.0) and exfoliative glaucoma (odds ratio per 1.0 μmol/l increase in homocysteine concentration = 1.3, 95% CI = 1.07–1.6) but was not a significant risk factor for normal-tension glaucoma (odds ratio per 1.0 μmol/l increase in homocysteine = 1.2, 95% CI = 0.9–1.6). These relationships were not affected substantially by adjustment for history of cardiovascular or peripheral vascular disease, race, age, or sex.

Hyperhomocysteinemia was present in similar percentages of patients with exfoliative glaucoma (56%) and patients with normal-tension glaucoma (52%, $P = .7$). However, logistic regression modeling of exfoliative glaucoma vs normal-tension glaucoma patients showed that an increased homocysteine concentration was a significant risk factor for exfoliation syndrome in the presence of glaucoma (odds ratio per 1.0 μmol/l increase in homocysteine = 1.2; 95% CI = 1.0–1.4).

DISCUSSION

HYPERHOMOCYSTEINEMIA REFERS TO A MILD TO MODERate elevation of the amino acid homocysteine in blood or plasma. In homocystinuria, a deficiency of cystathionine β-synthetase causes elevation of homocysteine, homocystine, and methionine in the serum and excessive excretion in the urine, with severe consequences.

We found elevated plasma homocysteine levels to be associated with exfoliation syndrome and exfoliative glaucoma when compared with healthy controls. In addition, increased homocysteine concentrations were predictive of exfoliative glaucoma when compared with normal-tension glaucoma patients. This finding suggests that the relationship between homocysteine levels and exfoliation syndrome is independent of the presence of glaucomatous optic neuropathy.

There were no significant differences in the prevalence of hypertension, peripheral or coronary artery disease, venous thrombotic events, and diabetes mellitus among groups studied. As expected from this lack of association, logistic regression modeling indicated that these variables were not operating as confounders, and adjustment for them in multivariate analyses had no impact on the primary result.

Hormone replacement affects plasma homocysteine levels.[16] Although the majority of patients in our study were women (58%), there was no significant difference in the frequency of patients under postmenopausal hormone replacement among patient groups.

Clear cut-off values and reference ranges for plasma homocysteine concentrations are currently not derived from prospective studies. The reference level used by our laboratory is based on a study that demonstrated increased mortality in patients with coronary artery disease who had plasma homocysteine levels higher than 9 μmol/l.[17]

Our results may help explain why hyperhomocysteinemia and exfoliation syndrome share common associations with various vascular disorders. Mild hyperhomocysteinemia is an independent risk factor for premature vascular disease[3] and is frequently found in patients with myocardial infarction,[4,18] stroke,[5] carotid intimal media wall thickening,[19] venous thrombosis,[20] end-stage renal disease,[21] and abdominal aortic aneurysm.[22] In the Blue Mountains Eye Study (Australia), exfoliation syndrome correlated positively with a history of hypertension, angina, myocardial infarction, or stroke.[6] Other studies have reported a higher frequency of exfoliation syndrome in patients with abdominal aortic aneurysm,[23] although this has been disputed,[24] and transient ischemic attacks.[25] Patients with exfoliative glaucoma have been reported to have lower baseline fingertip cutaneous capillary perfusion

than those with primary open-angle glaucoma or controls, longer time to maximal cold-induced flow reduction, and longer recovery time.[26]

Higher plasma homocysteine levels have been observed in patients with Alzheimer disease and vascular dementia.[8] Hagadus and coworkers (presented at the annual meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, May 1989) found a greater proportion of patients with early Alzheimer disease to have exfoliation syndrome compared with age-matched controls. Linner and associates[7] found 11 of 39 patients with dementia and cognitive impairment to have exfoliation syndrome. Recently, the Alzheimer peptide (Aβ) was detected in the aqueous humor of 38% of exfoliation syndrome patients undergoing cataract surgery.[27]

Hyperhomocysteinemia and exfoliation syndrome are also correlated with ocular vascular abnormalities. In exfoliation syndrome, anterior segment ischemia is prominent. Vessel lumens are often narrowed and may become obliterated, with marked alteration of the iris vasculature in advanced cases. Vessel dropout with collateral formation and iris hypoperfusion lead to patchy iris microneovascularization.[28] Friedburg and Bischof[29] found rubeosis in 50% of eyes with exfoliation syndrome, with an increased incidence in patients older than age 65. In clinically unilateral cases of exfoliation syndrome, ipsilateral pulsatile ocular blood flow and carotid blood flow have been reported to be reduced.[30] Blood flow velocities of the retrobulbar vessels are decreased in patients with exfoliative glaucoma compared with normal subjects.[31]

An association of exfoliation syndrome with branch and central retinal vein occlusion has been suggested.[9–11] Similarly, hyperhomocysteinemia was suggested to be a risk factor for retinal vein occlusion[12,13] and also for nonarteritic anterior ischemic optic neuropathy and central retinal artery occlusion.[14,15] We excluded patients with ocular vascular diseases to reduce the potential for a confounding of a relationship between exfoliation syndrome and hyperhomocysteinemia.

One could hypothesize that hyperhomocysteinemia might participate in the pathogenesis of exfoliation syndrome. High levels of plasma homocysteine have been demonstrated to cause vascular endothelial dysfunction, reduced bioavailability of nitric oxide, elastinolysis, and vascular muscle cell proliferation.[32,33] Homocysteine can induce the expression and synthesis of the tissue inhibitor of metalloproteinases-1 in a variety of cells ranging from vascular smooth muscle to hepatocytes and also promote activating protein-1 binding activity, which is critical for the induction of tissue inhibitor of metalloproteinases-1.[34,35] These findings suggest that homocysteine may alter extracellular matrix homeostasis on diverse tissue backgrounds besides the vascular wall.[34]

In exfoliation syndrome, it appears that a variety of unrelated epithelial and mesenchymal cell types may have a common metabolic lesion, resulting in the excessive and disordered synthesis of extracellular fibrillar material at multiple sites.[1] Previous studies indicate that exfoliation material contains extracellular matrix components (laminin, elastin, fibrillin).[36,37] Hyperhomocysteinemia may be associated not only with genetic determinants (thermolabile variant of methylene tetrahydrofolate reductase),[38] but also by other conditions such as age,[39] sex, renal failure,[20] medications,[40] and decreased uptake of vitamins B6, B12, and folate. In our study, the frequency of hyperhomocysteinemia in men was almost twice that in women. This finding is in agreement with the literature. Sex hormones and nutrition may explain this difference. Elevation of homocysteine appears to be at least as strong a risk factor for vascular disease in women as in men, even before menopause. We found no significant difference in sex among groups, reducing the possibility of confounding. One study estimated that inadequate plasma concentration of folate or one or more of the B vitamins account for two thirds of all cases of hyperhomocysteinemia in the elderly.[41] Given the great variability in the composition of many multiple vitamins, we excluded all patients taking these as supplements.

In conclusion, hyperhomocysteinemia was associated with exfoliation syndrome both with and without glaucoma. Hyperhomocysteinemia might be a modifiable risk factor for exfoliation syndrome. We suggest that plasma homocysteine measurement should be considered routinely in patients with exfoliation syndrome. Unlike other risk factors for exfoliation syndrome, hyperhomocysteinemia is readily reversible in most patients by taking inexpensive vitamin preparations containing vitamin B6, B12, and folic acid. A recent study demonstrated that folic acid (400 μg) associated with vitamin B6 and B12 can reduce homocysteine levels by 30%.[42] Randomized trials investigating the effects of lowering total homocysteine concentrations on hard, clinical cardiovascular endpoints are currently or soon to be under way.[43] Similar trials could be developed to evaluate the benefits of hyperhomocysteinemia treatment in the development of exfoliation syndrome.

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