

Homocysteine levels in plasma and sensorineural hearing loss in patients with pseudoexfoliation syndrome

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PURPOSE. *To determine the incidence and severity of hearing loss in different frequencies in patients with pseudoexfoliation. Furthermore, possible links between homocysteine and pseudoexfoliation were evaluated.*

METHODS. *Seventy-five consecutive patients with pseudoexfoliation and 75 sex- and age-matched subjects without pseudoexfoliation as control group were included in this prospective case-control study. Pure-tone audiometry was obtained in all subjects in both groups. Blood samples were obtained from 70 patients with pseudoexfoliation after overnight fasting for levels of homocysteine and analyzed by routine laboratory measurements.*

RESULTS. *Fifty-two (69%) patients with pseudoexfoliation and 39 (52%) controls had sensorineural hearing loss in speech frequencies. The difference between pseudoexfoliation and control group with regard to the frequency of sensorineural hearing loss in speech frequencies was statistically significant ($p=0.03$). No relationship was found between the degree of glaucomatous damage and hearing threshold variables in the patients with pseudoexfoliation glaucoma. Plasma homocysteine levels showed no significant difference when patients with pseudoexfoliation and hearing loss were compared with patients with pseudoexfoliation and normal hearing threshold ($p=0.5$). Hyperhomocysteinemia was found in 58% (29/50) of pseudoexfoliation patients with hearing loss, and 55% (11/20) of pseudoexfoliation patients with normal hearing threshold ($p=0.8$). No statistically significant correlation was found between plasma homocysteine and hearing loss in patients with pseudoexfoliation.*

CONCLUSIONS. *These findings suggest an association between sensorineural hearing loss and pseudoexfoliation in patients with pseudoexfoliation and glaucoma. The severity of hearing loss was not correlated with the degree of glaucomatous damage. There is no association between increased homocysteine levels and hearing loss in patients with pseudoexfoliation. (Eur J Ophthalmol 2006; 16: 542-7)*

KEY WORDS. *Audiometry, Glaucoma, Hearing loss, Homocysteine, Pseudoexfoliation*

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INTRODUCTION

Pseudoexfoliation syndrome (PXS) is an age-related disease in which abnormal fibrillar extracellular material is progressively produced and accumulated in ocular tissues (1-3). Pseudoexfoliation fibers have been discovered

in many visceral organs such as heart, lung, liver, gall bladder, kidney, and cerebral meninges (4-6). There is increasing evidence for systemic manifestations of PXS. The most mentioned manifestations are vascular diseases including history of angina, hypertension, or stroke and abdominal aortic aneurysms (7-10). PXS is more common

in patients with cerebrovascular or Alzheimer-type dementia (11). Recently, Cahill et al found that hearing loss is significantly more common in patients with PXS (12).

The source of blood supply of the inner ear is verte-brobasilar system. Circulatory disorders involving the verte-brobasilar system can cause hearing loss. Ischemic vascular damage of the inner ear is one of the known causes of sudden sensorineural hearing loss. Atherosclerosis is one of the factors that cause damage in organs like inner ear which are perfused by end-arterial system (13-15). Elevated total plasma level of amino acid homocysteine (tHcy) has been identified as an independent risk factor of arteriosclerosis, involving coronary, cerebral, and peripheral arteries and neurodegenerations (16-18). Recently, higher levels of plasma homocysteine in pseudoexfoliation syndrome were reported (19, 20). In addition, hyperhomocysteinemia may be a risk factor for noise-induced hearing loss (21, 22).

The purpose of this study was to determine the incidence and severity of sensorineural hearing loss in different frequencies in patients with pseudoexfoliation and to evaluate the possible correlation between plasma homocysteine level and hearing loss in patients with PXS and pseudoexfoliation glaucoma.

PATIENTS AND METHODS

We prospectively evaluated 75 consecutive patients with PXS and 75 age-matched subjects without any clinical signs of pseudoexfoliation in the Ophthalmology Department of Kocaeli University. Written informed consent was obtained from all patients.

Pseudoexfoliation is characterized by a dandruff-like material on the lens surface, pupillary border, anterior chamber angle, translucent defects in the peripupillary region, and decreased facility to dilate the pupil. All subjects had undergone a detailed eye examination before and after pupillary dilation by slit-lamp biomicroscopy and gonioscopy for the presence of pseudoexfoliation material in at least one eye, regardless of intraocular pressure. A detailed funduscopy examination was also performed on the patients with dilated pupil for evidence of glaucoma.

All patients with pseudoexfoliation were classified as PXS or pseudoexfoliation glaucoma according to intraocular pressure, cup-to-disc ratio, and visual field. The diagnosis of pseudoexfoliation glaucoma was made based on the combination of the following findings: an intraocular

pressure of >21 mm Hg, typical glaucomatous optic nerve changes (e.g., thinning or notching of the neural rim in the superior or inferior temporal area), and glaucomatous visual field defects. The glaucomatous visual field defects were identified as a cluster of three points in at least one hemifield reduced by 5 dB or more and including at least one point reduced by 10 dB or more, or a cluster of two points reduced by 10 dB or more, or three adjacent points on the nasal horizontal meridian that differed by 5 dB or more from their mirror points on the opposite side of the meridian. Patients with pseudoexfoliation glaucoma were classified into three subgroups according to the severity of the disease. Group 1 was the mild glaucoma group in which the mean deviation (MD) was between 5 and 8 dB, Group 2 was the moderate glaucoma group in which the mean deviation was between 9 and 16 dB, and Group 3 was the severe glaucoma group in which the mean deviation was >16 dB on full threshold testing according to the deviation level of the worse eye.

A detailed medical history was obtained to identify those with known or suspected diabetes mellitus, systemic hypertension, peripheral or coronary artery disease, venous thrombotic events, cerebrovascular disease, and current drug therapy. All patients underwent a complete ear, nose, and throat examination. Patients with any known ear diseases causing hearing impairment such as suppurative otitis media, mastoiditis, ototoxic drug use, audiovestibular diseases, major systemic illness, chronic alcohol abuse, immunosuppressive therapy, current use of cholesterol lowering agents, antidepressants, antimicrobial therapy, or vitamin supplements were excluded from the study.

Bilateral formal hearing test using pure-tone audiometer was performed on each subject. Determination of bone and air conduction thresholds was made at 500, 1000, 2000, 4000, and 8000 Hz. If the average of the pure-tone hearing thresholds obtained at 500, 1000, and 2000 Hz was 26 dB or more in at least one ear, it was defined as sensorineural hearing loss in speech frequencies. Pure-tone hearing threshold levels were classified according to threshold levels in speech frequencies of the worse ear: 0-25 dB, normal; 26-40 dB, minimal; 41-55 dB, mild; 56-70 dB, moderate; 71-90 dB, severe; 90 dB and more, total.

Five milliliters venous blood was collected in the fasting state from patients with pseudoexfoliation to measure plasma tHcy. The plasma tHcy level was measured using a fluorescence polarization immunoassay (Abbott IMx Homocysteine Assay, Abbott Laboratories). The normal val-

TABLE I - DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

	Pseudoexfoliation syndrome	Control
Age, yr, mean ± SD	68.25±7.41	66.76±8.15
Male/female	45/30	39/36
Glaucoma	42	—
Systemic hypertension	12	10
Diabetes mellitus	8	11

ue of the plasma tHcy was between 5 and 12 µmol/L according to the manufacturer. Patients were informed about their tHcy levels. Blood samples in five PXS patients were not measured because amount of blood was insufficient.

Statistical analysis

Data were analyzed by unpaired Student *t* tests and Bonferroni correction for continuous variables and Pearson χ^2 tests for categorical variables. Relationship be-

TABLE II - THE MEAN PURE-TONE THRESHOLDS OF PSEUDOEXFOLIATION AND CONTROL GROUPS AT SIX FREQUENCIES AND MEAN OF SPEECH FREQUENCIES (500, 1000, and 2000)

Pure tone thresholds (Hz)	Pseudoexfoliation (dB)	Control (dB)	p Value
Mean of speech	33.6±18.5	28.4±15.0	0.01
250	29.2±15.7	27.5±14.0	0.2
500	29.2±17.4	27.0±14.0	0.1
1000	31.1 ±17.8	27.2±15.8	0.4
2000	40.0±21.5	31.0±17.8	0.02
4000	54.3±25.4	47.5±21.6	0.04
8000	59.0±23.9	50.4±27.2	0.02

Values are mean ± SD

TABLE III - THE FREQUENCY OF SENSORINEURAL HEARING LOSS IN PSEUDOEXFOLIATION SYNDROME AND CONTROL SUBJECTS

	Pseudoexfoliation syndrome	Control	p Value
Hearing loss (speech frequencies)	52 (69)	39 (52)	0.03
Bilateral hearing loss (speech frequencies)	38 (73)	30 (76)	0.1
High frequency loss	69	59	0.01

Values are n (%)

TABLE IV - COMPARATIVE HOMOCYSTEINE LEVELS OF PSEUDOEXFOLIATION (PXS) PATIENTS WITH AND WITHOUT HEARING LOSS

	Subjects µmol±SD	Homocysteine level, (%)	Hyperhomocysteinemia
PXS with hearing loss	20	12.57±4.31	11 (55)
PXS without hearing loss	50	13.26±3.95	29 (58)
p Value		0.5	0.8

tween severity of hearing loss and degree of glaucomatous damage was evaluated by correlation analyses. All continuous variables were presented as a mean \pm SD. A *p* value of <0.05 was considered to indicate statistical significance.

RESULTS

The study included 75 patients with pseudoexfoliation and 75 age- and sex-matched control subjects without pseudoexfoliation. A total of 52 (69%) patients had bilateral and 23 (31%) patients had unilateral pseudoexfoliation. A total of 42 (56%) patients were diagnosed with pseudoexfoliation glaucoma. Demographic characteristics are listed in Table I. There were no significant differences between the groups according to age, sex, systemic hypertension, diabetes mellitus, or peripheral or coronary artery disease. No patient had any history of cerebrovascular disease or thromboembolism.

Sensorineural hearing loss in speech frequencies was found in 52 (69%) patients with PXS, and in 39 (52%) controls. There was a significant difference between PXS and control group with regard to the frequency of sensorineural hearing loss ($p=0.03$). The mean speech frequencies (average of pure tone hearing thresholds obtained at 500, 1000, and 2000 Hz) in the pseudoexfoliation group was 33.6 ± 18.5 dB, and control group was 28.4 ± 15.0 dB. The difference in mean speech frequencies between the pseudoexfoliation and control group was statistically significant ($p=0.01$). When the mean threshold values were compared, there were significant differences at 2000 Hz, 4000 Hz, and 8000 Hz (Tab. II). Bilateral hearing loss in speech frequencies was found in 30 subjects in the control group, and 38 patients in the PXS group ($p=0.1$) (Tab. III).

Hearing loss in high frequency was found in 69 (131 ears) patients with pseudoexfoliation, while it was found in 59 (110 ears) controls ($p=0.01$). Hearing loss was classified according to the speech threshold levels of the worse ear. There were 30 patients with minimal, 11 patients with mild, 6 patients with moderate, 3 patients with severe, and 2 patients with total hearing loss in PXS group. When the control group was evaluated according to hearing loss, 26 patients had minimal, 8 patients had mild, 3 patients had moderate, and 2 patients had severe hearing loss. Severity of hearing loss was not different between pseudoexfoliation and control subjects ($p=0.2$).

When hearing loss in speech frequencies was evaluated in the pseudoexfoliation glaucoma patients and the PXS patients, it was found that 21 patients ($n=33$) with PXS and 31 patients ($n=42$) with pseudoexfoliation glaucoma had hearing loss. There was no significant difference between these two groups. The correlation between the severity of hearing loss and degree of glaucomatous damage was also not observed.

Because the mean age of the patients in the pseudoexfoliation group was slightly but not statistically significantly higher than that of the control subjects, the patients with pseudoexfoliation were divided into two subgroups according to age: those 68 years or older and those 67 years or younger. Twenty-four of 35 (68%) patients age 67 years or less and 27 of 40 (67%) patients age 68 years or more (subgroups in patients with pseudoexfoliation) had sensorineural hearing loss in speech frequencies. There was no statistically significant difference in frequency of hearing loss among the subgroups.

Plasma homocysteine levels in PXS patients with hearing loss showed no statistically significant difference when compared with pseudoexfoliation patients having normal hearing threshold ($p=0.5$). Hyperhomocysteinemia was present in 58% (29/50) of pseudoexfoliation patients with hearing loss and 55% (11/20) of pseudoexfoliation patients having normal hearing threshold ($p=0.8$) (Tab. IV). The correlation between plasma homocysteine levels and degree of hearing loss was also evaluated in patients with pseudoexfoliation. However, no statistically significant correlation was found between plasma homocysteine levels and degree of hearing loss in patients with pseudoexfoliation.

DISCUSSION

In the current study, we found that there is a significant sensorineural hearing loss at speech and high frequencies in PXS and pseudoexfoliation glaucoma patients when compared with controls. No statistically significant correlation was found between plasma homocysteine levels and hearing loss in pseudoexfoliation patients.

Hearing loss has been identified as one of the most frequent conditions affecting the older population, with a reported prevalence between 39% and 54% of adults in various populations (23-25). In this study, hearing loss was observed in 52% of controls. In all series, the prevalence of hearing loss was increasing with age. The Epi-

demiology of Hearing Loss study reported an increased prevalence of measured hearing loss from 21% of people aged 48 to 59 years to 90% of those aged >80 years (26). In the literature, prevalence studies have reported prevalence of hearing loss using the ear with better hearing. Higher frequency of hearing loss in controls than in previous studies could be explained regarding these differences in the current study.

Cahill et al (12) have reported that PXS is associated with sensorineural hearing loss using 1000, 2000, and 3000 Hz pure-tone hearing thresholds. We evaluated the patients' hearing loss at six different frequencies. There was statistically significant hearing loss at 1000, 2000, 4000, and 8000 Hz. Our study suggests that hearing loss was found not only at speech frequencies, but also at high frequencies in patients with pseudoexfoliation.

The fact that pseudoexfoliation and hearing loss share common predisposing factors implies that there are similarities in the pathologic and biochemical findings of the two conditions. Hearing loss and pseudoexfoliation are essentially age-related diseases. Presbycusis is bilateral, degenerative hearing loss associated with aging. The hearing loss in presbycusis is more severe in the higher frequencies. Presbycusis is thought to be the result of the cumulative effects of several harmful situations during life, including ototoxicity, noise, and genetically influenced degeneration (13, 17, 18). PXS is a systemic disease involving connective tissue of various visceral organs such as heart, lung, liver, kidney, and meninges (7, 8). It might be speculated that deposition of pseudoexfoliation materials within the cochlea might cause hearing loss in pseudoexfoliation patients. Further studies at the cellular and molecular level are needed to be done to elucidate the mechanisms of hearing loss.

Hyperhomocysteinemia, a risk factor for vascular diseases such as cerebrovascular and cardiovascular disease, may be associated with PXS and glaucoma, which may partially explain the increased risk of vascular diseases among patients with pseudoexfoliation (19, 20, 27). A significant association between pseudoexfoliation and hearing loss found in this study implies that systemic vascular diseases probably play a significant role in hearing loss. The homocysteine levels were increased in patients with noise-induced hearing loss. A weak correlation between age-related hearing loss and homocysteine level was also found (21, 22). In this study, no statistically significant correlation was found between plasma homocysteine levels and hearing loss in patients with pseudoexfo-

liation. Elevation of homocysteine may partly explain the increased risk of vascular diseases among patients with pseudoexfoliation; however, we believe that there is no association between increased homocysteine levels and hearing loss in patients with pseudoexfoliation.

In this study, the difference in the frequency of hearing loss in patients with PXS and patients with pseudoexfoliation glaucoma was not statistically significant. There was no significant correlation between the severity of hearing loss and degree of glaucomatous damage. Some studies have suggested a relationship between glaucoma and sensorineural hearing loss; others have found no evidence for an association (13-15). Pseudoexfoliation glaucoma is both clinically and histopathologically different from primary open angle glaucoma. Hayreh et al (28) reported that there is no association between hearing loss and ocular and optic nerve head ischemic disorders. Cahill et al (12) found no significant relationship between the presence of glaucoma and hearing loss in patients with PXS. This finding suggests that the hearing loss in PXS is not related to the presence of glaucomatous optic neuropathy.

This study demonstrates that there is an association between sensorineural hearing loss and pseudoexfoliation. However, there is no association between increased homocysteine levels and hearing loss in patients with pseudoexfoliation. Therefore, further studies using a greater number of samples with a longitudinal fashion are necessary to clarify the relationship between sensorineural hearing loss and pseudoexfoliation syndrome.

No authors have any proprietary interest.

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