Sensorineural Hearing Loss in Pseudoexfoliation Syndrome

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Purpose: To determine hearing thresholds at sound frequencies important for speech comprehension in subjects with ocular pseudoexfoliation (PXF) and to compare them with that of controls without PXF.

Methods: Eighty-three subjects with ocular PXF and 83 age and sex matched controls without PXF were enrolled in this case-control study. Pure tone audiometry (bone conduction) was performed at 1, 2 and 3 kilohertz (KHz) in all subjects. Thresholds were compared to an age and sex stratified standard (ISO7029) and between study groups. Hearing loss was defined as sum of tested hearing thresholds (HTL-1,2,3) lower than the ISO7029 standard median.

Results: The study included 60 male and 23 female subjects in each group. Hearing loss was present in 147 of 166 (88.6%) of examined ears in the case group vs 89 of 166 (53.6%) in the control group (P<0.001; odds ratio [OR] = 6.69; 95% confidence interval [CI], 3.49-11.79). Overall 78 subjects (94.0%) in the case group vs 58 subjects (69.9%) in the control group had hearing loss in one or both ears (P< 0.001; OR=6.72; 95%CI, 2.42-18.62). Hearing thresholds at each of the examined frequencies and the HTL-1,2,3 were also significantly higher in individuals with PXF. Although glaucoma was significantly more common in subjects with PXF (51.8% vs 22.9%, P<0.001), it was not associated with hearing loss in any of the study groups.

Conclusions: Hearing thresholds at frequencies which are important for speech comprehension are significantly worse in individuals with ocular PXF as compared to matched controls. This finding may support the multi-organ nature of PXF syndrome.

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INTRODUCTION

Ocular pseudoexfoliation (PXF) syndrome is characterized by white fibrillar deposits on anterior segment structures particularly evident on the iris, lens capsule and trabecular meshwork. PXF is usually found in eyes of individuals over age 50 with a prevalence ranging from 0.4 to 24% in different studies.[1-3] This condition may be asymptomatic and diagnosed incidentally during routine ophthalmologic examinations. Histopathologically, PXF deposits are composed of periodic acid Schiff positive and Congo-red positive material resembling amyloid. Ultrastructurally, these deposits contain microfibrils measuring 8-10 nm in diameter composed of laminin, fibrilin, alpha-elastin, fibronectin, heparin and chondroitin sulfate.[1]

Ocular PXF syndrome is of great importance to the ophthalmologist; zonular weakness and capsular fragility are of particular concern during cataract surgery and both chronic open angle and angle closure glaucoma have been associated with PXF syndrome. PXF-like deposits have also been found in other organs and tissues such as the heart, lung, liver, kidney, meninges, and skin.[4-7] Additionally, there is evidence of association between PXF and systemic vascular disorders including systemic hypertension, abdominal aortic aneurysms, ischemic heart disease, Alzheimer's disease and ocular vascular abnormalities such as retinal vascular disorders and age-related macular degeneration.[8-14]

The correlation between glaucoma and hearing loss has been previously studied, but except for normal tension glaucoma and some congenital syndromes, no strong evidence is available for such an association.[15-17] Our clinical impression has been that patients with PXF have significant hearing disability which has also been described by other investigators.[18-20] Considering the structural characteristics of hearing organs and the possible adverse effect of abnormal deposits and/or vascular abnormalities on these organs, such a finding would not be surprising. We conducted the current study to evaluate the possible correlation between PXF syndrome and sensorineural hearing loss.

METHODS

This case-control study included patients with evidence of ocular PXF and an equal number of age and sex matched controls. The ethics committee of the institute approved this project and informed consent was obtained from all cases. All subjects were interviewed and underwent a complete ophthalmologic examination including determination of best-corrected Snellen visual acuity, slitlamp examination, Goldmann applanation tonometry, gonioscopy and dilated ophthalmoscopy using a +90 D non-contact lens. The presence of PXF material on the iris, lens capsule, angle or corneal endothelium was confirmed by one of the investigators (SY). Patients were stratified into age and sex groups and matched controls were selected and screened for absence of PXF material by the same investigator.

Glaucoma was diagnosed based on presence of at least two of the three following criteria: (1) intraocular pressure >22 mmHg without antiglaucoma medications; (2) typical glaucomatous optic nerve head damage; and (3) presence of glaucomatous visual field defects which were defined on the basis of Anderson's criteria[21] (i.e. a cluster of 3 non-edge points on the pattern deviation plot in standard achromatic perimetry using the Humphrey device, 2 of which depressed with probability less than 5% and one depressed with probability less than 1%; abnormal glaucoma hemi-field test; pattern standard deviation less than 5%). To prevent any confusion in terms of glaucoma diagnosis and terminology, only patients with at least one definitely glaucomatous eye and those who were non-glaucomatous were enrolled; glaucoma suspects (subjects with only one of the above diagnostic criteria) were not included in the study. Any subject with manifestations of PXF or with evidence of glaucoma in either eye was considered a case of PXF syndrome and glaucoma respectively.

Patients were excluded if there was history of acute or chronic ear disease, head trauma, long term exposure to heavy noise or gunfire and intake of ototoxic agents such as gentamicin or streptomycin. All subjects were referred to an otolaryngologist who examined them and excluded cases with evidence of upper respiratory tract infection and external or middle ear abnormalities. One masked operator performed standard bilateral pure-tone audiometry (PTA) using the same device for all subjects. Hearing thresholds were determined using PTA in bone conduction at 1, 2 and 3 KHz, frequencies which are thought to be important for speech comprehension. Testing was started 40 dB above the expected thresholds and repeated at 10 dB decrements. Thresholds were determined when subjects

could hear at least 2 of 3 stimuli. The sum of these thresholds (hearing threshold level at 1, 2 and 3 KHz= HTL-1,2,3) was compared with the ISO7029 standard. This standard is the result of a meta-analysis of large community based studies to determine the normal distribution of hearing thresholds at different frequencies in otologically normal white subjects. Hearing loss was defined if HTL-1,2,3 was higher than the sum of corresponding normal median thresholds as determined by the ISO7029 standard. The rate of hearing loss in one or both ears was compared between cases and controls, furthermore, average hearing thresholds at each frequency was compared between cases and controls.

Overall 166 subjects were required based on sample size calculation with study power set at 90% and alpha error at 5%. Data was analyzed using unpaired student *t* test for continuous variables and Chi square test for categorical variables. A P value of <0.05 was considered to indicate statistical significance.

RESULTS

Overall, 166 subjects were enrolled in this case-control study which included 83 patients with PXF syndrome and 83 age and sex matched controls (60 male and 23 female subjects in either study groups). Mean age of male participants was 69.2±7.98 and 69.0±7.92 years in cases and controls respectively (P=0.88). Corresponding figures for female participants were 72.4±6.62 and 72.0±5.85 years (P=0.83). Further details regarding age and sex are presented in table 1. Of 83 subjects with PXF, 24 (28.9%) had unilateral and 59 (71.1%) had bilateral PXF.

Hearing loss, defined as HTL-1,2,3 higher than the ISO7029 median, was significantly more prevalent in ears of cases versus controls; hearing loss was present in 147 of 166 (88.4%) examined ears in the case group versus, 89 of 166 (53.6%) examined ears in the control group (P<0.001; odds ratio [OR]= 6.69; 95% confidence interval [CI], 3.49-11.79). The study groups were compared for hearing loss in either ear of individuals (according to the above-mentioned definition) which also demonstrated a significantly higher prevalence of hearing loss in patients with PXF: 78 subjects (94.0%) in the case group versus 58 subjects (69.9%) in the control group had hearing loss in one or both ears (P<0.001; OR=6.72; 95%CI, 2.42-18.62). To compare cases and controls directly, mean hearing thresholds at each of the examined frequencies and the total threshold were compared between the study groups which revealed significantly higher thresholds in individuals with PXF as compared to control subjects (table 2).

Table 1 Demographic characteristics

Age group (year)	Male (No.)		Female (No.)	
	Case	Control	Case	Control
50-54	3	3	0	0
55-59	6	6	0	0
60-64	5	5	2	2
65-69	16	16	5	5
70-74	13	13	7	6
75-79	10	10	7	8
80-84	7	7	2	1
85	0	0	0	1
Total	60	60	23	23

Table 2 Mean hearing thresholds

Frequency	Cases (dB)	Controls (dB)
1 KHz	29.1±20.0	17.1±15.2
2 KHz	37.0±20.9	22.5±17.1
3 KHz	46.9±21.8	33.8±20.1
HTL-1,2,3	112.6±57.1	72.6±46.9

HTL 1,2,3: sum of hearing threshold level at 1, 2 and 3 KHz

• *t* test, P<0.001

Glaucoma was present in one or both eyes of 43 (51.8%) cases and 19 (22.9%) controls (P<0.001), however the presence of glaucoma was not associated with hearing loss in any of the study groups. In the case group, 41 out of 43 (95.3%) patients with glaucoma and 37 out of 40 (92.0%) of non-glaucomatous subjects suffered from hearing loss in one or both ears

(P=0.65). In comparison, 15 out of 19 (79%) patients with glaucoma and 43 out of 64 (67%) non-glaucomatous subjects in the control group had hearing loss in one or both ears (P=0.48).

DISCUSSION

The present study demonstrated a significantly higher prevalence of sensorineural hearing loss in subjects with PXF as compared to an age and sex matched control group. This higher prevalence was observed both in comparison to a population based standard and by comparison absolute hearing thresholds in cases and controls. The frequencies selected in this study (1000, 2000 and 3000 Hz) are considered important for speech comprehension and probably reflect the functional status of the individual.

Other studies have also demonstrated a higher prevalence of sensorineural hearing loss in patients with PXF. In an uncontrolled study, Cahill et al[18] performed pure tone audiometry at 1, 2 and 3 KHz for 69 subjects with PXF and reported HTL-1,2,3 higher than the ISO7029 median in 73.7% of studied ears. Since this study lacked a control group and assuming that in a "normal" population one expects 50% of subjects to have values on either side of the median, it may be concluded that this figure reflects abnormally high hearing thresholds in individuals with PXF. Shaban and Asfour[19] conducted a similar uncontrolled study and also reported higher than standard (ISO7029) hearing thresholds in 36 of 41 subjects (87%) with PXF. Aydogan et al[20] examined 75 subjects with PXF and 75 controls, performing PTA at 250, 500, 1000, 2000, 4000 and 8000 Hz. In their study, mean thresholds at speech frequencies (average of thresholds at 500, 1000 and 2000 Hz) was higher in cases than controls. Mean absolute hearing thresholds at 2, 4 and 8 KHz were also higher in cases than controls, however absolute hearing thresholds at 250, 500 and 1000 Hz, individually did not differ significantly between cases and controls. The advantages of our study compared to previous ones include a larger number of subjects and selection of a well-matched control group which also included a considerable number of subjects with glaucoma.

Sensorineural hearing loss and presbyacusis may be attributed to various etiologies such as toxic agents, acoustic trauma or the aging process; however, the exact mechanism is unknown.[22,23] Based on reports demonstrating PXF deposits in visceral organs, one may postulate the sensorineural hearing loss in PXF syndrome to be due to deposition of PXF material on the organs of corti causing dysfunction in hearing mechanoreceptors. This deposition may cause slight alterations in fine vibrations induced by sound such as that observed in the eye in the form of phacodonesis. Alternatively or working in association with the first purported mechanism, it is possible that vascular compromise may play a role in the hearing loss. The association of cardiovascular disorders,[8-11] decreased blood flow velocity and increased vascular resistance in middle cerebral arteries[24] and evidence of impaired vascular endothelial cell function[25] in patients with PXF may support this theory.

No definite correlation between glaucoma and hearing loss has been demonstrated yet.[16] In Cahill and coworkers' study,[18] the proportion of ears with hearing loss was not significantly different on the side of the eye without PXF, with PXF but not glaucoma, and with PXF and glaucoma. In both Shaban and Asfour's[19] and Aydogan's[20] studies there was also no significant difference in the frequency of hearing loss between cases with and without glaucoma. These findings are similar to our results which revealed no correlation between glaucoma and hearing loss in any of the study groups.

By demonstrating the higher prevalence of sensorineural hearing loss in PXF syndrome, the findings of the present study and others imply that this apparently ocular disorder may truly be a manifestation of a systemic condition which affects multiple organs and tissues throughout the body. The disability caused by hearing impairment, even in one ear leading to loss of stereoacusis, may have a major impact

on the functional capacity of aging individuals. By considering hearing loss as one abnormality in PXF syndrome, ophthalmologists may have a chance to provide rehabilitation for patients beyond their field.

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