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Hearing Evaluation in Patients with Exfoliative and Primary Open-Angle Glaucoma

Vassiliki P. Paliobei, MD, PhD¹, Georgios K. Psillas, MD, PhD¹, Dimitrios G. Mikropoulos, MD, PhD², Anna-Bettina Haidich, PhD³, Jannis Constantinidis, MD, PhD¹, and Anastasios G. P. Konstas, MD, PhD²

Abstract

Objective. The aim of this prospective study was to audiologically evaluate consecutive glaucoma patients with or without exfoliation.

Study Design. Prospective study.

Setting. Glaucoma Unit and Audiology Department at a university hospital.

Subjects and Methods. Consecutive subjects with exfoliative glaucoma (XFG) or primary open-angle glaucoma (POAG) aged between 50 and 70 years were enrolled. Auditory thresholds at 0.5, 1.0, 2.0, 4.0, and 8.0 Hz were measured bilaterally. Cochlear activity was assessed by recording distortion product otoacoustic emissions (DPOEs). Functional changes in the retrocochlear auditory pathway were evaluated by auditory brainstem responses (ABRs).

Results. One hundred and ten patients with XFG and 85 patients with POAG who presented in a glaucoma clinic were investigated. The mean age of study patients was 66.2 ± 5.6 years; range, 50-70 years. The odds of pathologic ABR central transmission time (interpeak latencies I-III, III-V, and I-V and waves I, III, and V) were 4.34 times higher in patients with XFG than in patients with POAG (95% confidence interval [CI], 2.22-8.49; P < .001). This significant association remained after adjusting for sex and age (odds ratio [OR] 4.12; 95% CI, 2.07-8.22; P < .001). Furthermore, the odds of ABR remained significantly higher in patients with XFG than in patients with POAG (OR 4.36; 95% CI, 2.10-9.06; P < .001) after controlling for systemic diseases (arterial hypertension, coronary heart disease, high cholesterol, and stroke).

Conclusion. In the first study to compare XFG and POAG monitoring of the peripheral and central auditory pathway, it has been documented that XFG patients show a greater prevalence of retrocochlear pathology.

Keywords

pure-tone audiometry, auditory brainstem responses, retrocochlear, ISO 7029
especially at high frequencies. However, the relationship between hearing loss and glaucoma is not clear, and there are contrasting results from previous studies. No controlled study has been performed directly comparing patients with XFG and patients with primary open-angle glaucoma (POAG) (ie, glaucoma patients with and without exfoliation). Such a comparison may improve our understanding of the occurrence and pathobiology of hearing loss in patients with glaucoma (XFG and POAG).

Because XFS is now considered an age-related systemic condition, the possibility arises that it may involve the ear apparatus, causing hearing loss. If such a hypothesis is valid, the ophthalmologist should involve the ear, nose, and throat specialist in a multidisciplinary approach to the care of these patients.

The aim of this prospective study was to evaluate the function of peripheral and central auditory pathway in subjects with XFG and to determine the relationship between XFG/POAG and hearing loss. We also wished to document whether the pathology in XFG patients was at a cochlear or retrocochlear level. Because conventional audiometric tests are not sensitive enough to detect the initial phase of sensory loss or capable of determining the site and pattern of this impairment, the current investigation was performed by tonal audiometry as well as the electrophysiologic procedures of ABRs and evoked otoacoustic emissions.

Methods

The research protocol was approved by the Bioethics Committee of the Medical School of Aristotle University of Thessaloniki. Informed consent was obtained from all participants before they entered the study. Consecutive white XFG or POAG patients were recruited from the Glaucoma Unit of the 1st University Department of Ophthalmology, AHEPA Hospital, Thessaloniki, Greece. All XFG and POAG patients who agreed to participate and met the inclusion and exclusion criteria were enrolled in the study. Inclusion criteria were age between 50 and 70 years; best corrected distance Snellen visual acuity greater than 0.1 in the study eye; typical glaucomatous disc damage and reproducible glaucomatous visual field loss with a mean deviation greater than –4.0 dB in the study eye (with Humphrey 24-2 SITA standard automated perimetry); open anterior chamber angles; and untreated baseline intraocular pressure greater than 22 mm Hg at 10:00 AM (+1 hour). In the XFG group, all patients exhibited the typical clinical manifestations of XFG: exfoliation material deposition in the anterior segment of the eye. In the POAG control group, all patients demonstrated the standard clinical evidence for POAG, whereas a comprehensive slit lamp examination did not reveal any signs of exfoliation material deposition.

Subjects with a history of middle ear disease, noise-induced trauma, exposure to ototoxic drugs, head/ear trauma, or a family history of deafness were excluded from the study. Additional exclusion criteria were evidence of uveitis, otosclerosis, known congenital or hereditary abnormalities, previous use of corticosteroids, tumor in the region, clinical evidence of viral or bacterial infection (eg, labyrinthitis, meningitis), evidence of presbycusis, known history of diabetes, hypothyroidism, and a prior diagnosis of systemic autoimmune disease.

All study subjects underwent the same ear, nose, and throat examination and received a standard battery of age-appropriate hearing tests, including pure-tone audiometry, performed using an audiometer, tympanometry, and stapedial reflex tests. Pure-tone hearing thresholds were measured at 0.25, 0.5, 1, 2, 4, and 8 kHz for each ear with a GSI-61 (Grason-Stadler, Minnesota; King of Prussia, Pennsylvania; Welch Allyn Inc, Skaneateles Falls, New York) audiometer. Tympanograms and acoustic reflex were performed with a GSI-33 (Grason-Stadler, Welch Allyn). Normal hearing was defined as −5 to +20 dB and hearing level across all of the frequencies.

Auditory brainstem responses (ABRs) were recorded with Amplaid MK12 (Biomedical Line, Amplifon, Milan, Italy) in both groups of glaucoma patients. The ABR measurements were performed in a sound-treated room using click stimulation at rates of 11/s of alternating polarity for 10 milliseconds and filtered between 30 and 2500 Hz at 70 and 90 dB nHL. The ABR interpeak intervals (IPLs) for each study patient were compared with published norms for adults. ABR latencies from normal-hearing adults in our clinic corroborate favorably with these published norms (Table 1). Each ear was tested individually, and the parameters studied were the absolute latency of waves I, III, V; the IPLs I-III, III-V, I-V; and the interaural relation of the latency of wave V.

Distortion product otoacoustic emissions (DPOAEs) were recorded using AccuScreen (Madsen, GN Otometrics, Taastrup, Denmark) to assess cochlear function.

In patients with clinical signs of dizziness, vestibular tests were carried out to identify vestibular pathology. In patients with pathological ABR morphology, we carried out magnetic resonance imaging (MRI) scan to detect the presence of ischemic lesions.

The audiometric frequencies were converted to α coefficients using the equation in ISO 7029. These coefficients were compared with the ISO 7029 standard for each gender and frequency using Student t test. The α coefficients between POAG and XFG patients were compared by the Student t test. Logistic regression analysis was performed for the association of pathologic ABR and type of glaucoma. The unadjusted odds ratios and adjusted odds ratios are presented. The association of pathologic ABR wave latencies and glaucoma type

| Table 1. Normative Data for Adult Auditory Brainstem Responses (ABRs) According to Our Laboratory Results |
|----------------|---------------|--------|
| ABR Component | Mean, ms     | SD, ms |
| I              | 1.53          | 0.07   |
| III            | 3.74          | 0.14   |
| V              | 5.51          | 0.15   |
| I-III          | 2.18          | 0.13   |
| III-V          | 1.78          | 0.22   |
| I-V            | 3.96          | 0.30   |

Rate 11/s, intensity 70 dB HL, repetitions 1000, analysis time 10 ms.
was assessed with the chi-square test or the Fisher exact test, as appropriate. All reported \( P \) values were 2-tailed, with \( P < .05 \) considered as significant; analyses were conducted using SPSS 17 (SPSS, Inc, Chicago, Illinois).

**Results**

The study included 110 consecutive XFG patients (220 ears) and 85 consecutive POAG patients (170 ears). The mean age of study cohort was 66.2 ± 5.6 years (range, 50-70 year). The mean age of the XFG group was 67.4 ± 4.6 years and of the POAG group 64.8 ± 6.5 years. The proportion of women was lower in the XFG group (41.8%, 46/110) than in the POAG group (55.3%, 47/85).

The \( \alpha \) coefficient was significantly higher in XFG patients compared with the norms provided by the ISO 7029 standard at all frequencies for both genders. In POAG patients, the \( \alpha \) coefficients were significantly higher compared with the norms of the ISO 7029 at all frequencies in female patients. In male POAG patients, the \( \alpha \) coefficients were significantly higher compared with the norms given in the ISO 7029 at the frequencies 0.25, 0.50, 1.0, and 2.0 kHz but not for the higher frequencies 4.0 and 8.0 kHz. In the POAG group, the \( \alpha \) coefficient was significantly lower compared with XFG-only in male patients at the 2.0 kHz frequency. These results are graphically displayed in Figure 1.

Within the XFG group, those with pathologic ABR demonstrated significantly higher thresholds in frequencies 0.25, 4, and 8 kHz as well as in the mean pure-tone average (PTA) at 0.5, 1.0, 2.0, 4.0, and 8.0 compared with the normal ABR (Table 2) after adjustment for age. In the POAG group, there were no significant differences in any of the thresholds investigated.

The odds of pathologic ABR central transmission time (interpeak latencies I-III, I-V, wave V) were 4.34 times higher in patients with XFG than in those with POAG (95% confidence interval [CI], 2.22-8.49, \( P < .001 \); Table 3). This significant association remained after adjustment for sex, age, arterial pressure, coronary heart disease, cholesterol, and stroke history (odds ratio [OR] 4.36; 95% CI, 2.10-9.06, \( P < .001 \)).

In the XFG group, patients with pathologic ABR exhibited significantly higher thresholds in frequencies 0.25, 4, and 8 kHz as well as for the mean PTA compared with patients with normal ABR. In contrast, no significant differences in any of the thresholds studied were found for POAG patients. Overall, the ABR pathological findings (prolonged interpeak latencies I-V or absence of V wave) were more common in XFG than in age-matched POAG patients, an observation that supports the theory of an unknown retrocochlear causative factor located at the brainstem.

Prolongation of the ABR V and I-V IPLs was common in XFG patients: distortion/absence of V occurred in 60.6% versus 34.9% of the POAG group (\( P = .01 \)), whereas prolongation of I-V IPL occurred in 36.4% of XFG subjects versus 7.5% of those with POAG (\( P = .716 \)). Prolongation of the ABR I-III IPL and distortion/absence of wave III were occasionally seen in the XFG group, occurring in 12.1% (\( P = .029 \)) and 15.1% (\( P = .030 \)) of patients, respectively, as opposed to none of the POAG patients. No difference was seen in absent waveforms, which were isolated in 30.3% and 28.6% of the XFG and POAG patients, respectively (\( P = .375 \)).

The mean DPOAE amplitudes were reduced in the region of high frequencies for both glaucomas, with high frequency hearing loss greater than 50 db determined by pure-tone audiometry. For the other patients, the results were inconsistent, so they are not reported. No abnormal signs were detected in Figure 1.

![Mean \( \alpha \) at increasing audiometric frequencies in primary open-angle glaucoma (POAG) group (solid line with circles) and exfoliation syndrome (XFS) group (solid line with triangles) and the ISO normative coefficients for comparison (dotted line with the bowknot symbol) in (A) males and (B) females.](oto.sagepub.com)

**Figure 1.** Mean \( \alpha \) at increasing audiometric frequencies in primary open-angle glaucoma (POAG) group (solid line with circles) and exfoliation syndrome (XFS) group (solid line with triangles) and the ISO normative coefficients for comparison (dotted line with the bowknot symbol) in (A) males and (B) females.
MRI scans of the brains of those XFG or POAG patients with abnormal ABRs.

Discussion

There is inconclusive evidence on the correlation between glaucoma and hearing loss, given the diverse pathogenesis of glaucoma and the varied methods used in previous investigations.16-18 The current investigation has confirmed the impressions of previous researchers that glaucoma is correlated with hearing loss. In both glaucoma groups investigated (XFG and POAG), our results consistently show a degree of hearing loss at most of the tested frequencies. Importantly, in XFG patients, hearing impairment was far more prevalent. To the best of our knowledge, this is the first controlled study to compare XFG and POAG with regard to hearing status by electrophysiological evaluation of the auditory nerve and the auditory brainstem function in a sufficiently large patient cohort.

A previous study11 evaluating pure-tone audiograms detected sensorineural hearing loss for frequencies of 1, 2, and 3 kHz in a consecutive group of 69 patients with XFS. Other studies8-10 have evaluated pure-tone audiograms in XFS and age- and gender-matched control patients and have confirmed the correlation between XFS and sensorineural hearing loss.

Advantages of the current study are the inclusion, for the first time, of a sufficiently large cohort of XFG and POAG patients and the selection of a suitable age- and gender-matched control group. The auditory thresholds in both POAG and XFG groups were higher than expected from the ISO 7029 international standards and are in agreement with previous reports concerning cochlear involvement.8-12

According to Ritch and Schlötzer-Schrehardt,1 the hearing loss connection in glaucoma is interesting because the cells in the ear that produce and drain endolymph are structurally analogous to the anterior segment cells in the eye that produce and drain aqueous humor. Similar parallels are found in the brain, where the choroid plexus and the arachnoid villi are structurally analogous to the ciliary epithelium and the trabecular meshwork.

Ultrastructurally, fibrils identical to those seen in XFG have been demonstrated in the basement membranes and extracellular matrices of extraocular tissues such as the brain, the choroid plexus and the arachnoid villi, the skin, and several visceral organs.19 A number of reports have suggested that accumulation of exfoliation material aggregates in the vessel walls and may be associated with an increased risk for vascular disease.

There is a common embryological origin between the anterior segments of the eye and the tectorial membrane of the inner ear from neural ectoderm, and their structure similarly involves type V collagen fibers. If the organ of Corti is also involved in XFG and is a site for exfoliation deposition, this could disturb its chemical environment and result in

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<th>Table 2. Comparison of Hearing Thresholds Between Pathologic and Normal ABR in XFG and POAG Patients</th>
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<th>Table 3. Association of ABR Transmission Time and Glaucoma Type</th>
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<td>ABR, n (%)</td>
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Abbreviations: ABR, auditory brainstem response; POAG, primary open-angle glaucoma; PTA, pure-tone average; XFG, exfoliation syndrome.

*Odds ratio adjusted for sex, age, diabetes, arterial pressure, coronary heart disease, cholesterol, and stroke.
sensorineural hearing loss. This process conceivably may lead to a change of fluid homeostasis, which could cause tinnitus or even endolymphatic hydrops. The latter hypothesis supported by the findings of Turgut et al but was not supported by our evidence because XFG patients were negative for vestibular pathology.

Numerous investigations have provided a consensus of opinion that associates XFG with an increased prevalence of vascular disease. The fact that the cochlea and the vestibule are supplied by arteries from the same source, namely, the internal auditory artery—which commonly arises from the anterior inferior cerebellar artery, a branch of the basilar artery, and, in some individuals, directly from the basilar artery—might also support a vascular cause of hearing loss in XFG. It is relevant that Balley-Moulinier et al showed an abnormal elevation of the intervals I-III, III-V, and I-V in ischemic patients. Furthermore, Lynn and Gilroy demonstrated that 13 of 14 patients with vertebrobasilar artery occlusive disease showed either increased IPLs I-III and III-V or no identifiable waves III, IV, and V. These findings support the notion that the higher incidence of pathological ABR findings in XFG is attributable to vascular pathology.

Several studies have been conducted to evaluate the effect of age on latencies of the ABR. Some investigators have reported a significant effect, whereas others have reported no effect at all. An increase in latency would only be expected if thresholds are elevated, and there is nothing to suggest that aging per se influences the interpretation of latency information in the ABR. Although the mean age of our study XFG patients was 67.4 ± 4.6 years, the statistical analysis showed significantly higher prevalence of ABR pathology in XFG versus POAG regardless of the age parameter.

The results of the present study showed that wave V and the I-V interpeak latency were significantly longer in XFG patients than in age-matched POAG patients. The interaural difference of the latency of wave V was calculated and the mean interaural differences of this latency in XFG and POAG patients were higher than 0.4 and less than 0.3, respectively, which was highly abnormal for 60.6% of our XFG patients with ABR pathology. The role of interaural difference of the V-wave latency in the diagnosis of cochlear and retrocochlear diseases has been pointed out by Wieland and Kemp, Hood, and Hall. It is therefore reasonable to assume that the abnormal ABR responses together with the hearing losses that were revealed by our study are indicative of either XFG-related alterations in the central auditory nervous system or an altered central activity due to changes in the output of the auditory periphery.

Given that the coexistence of pathologic ABR central transmission time and sensorineural hearing loss in pure-tone audiometry is relatively common in XFG patients, it is more likely that the latency prolongation reflects a slowing of the synaptic processes to the organ of Corti or decreased neural conduction velocity in the first auditory neuron, which disrupts the neural synchrony necessary for the ABR generation. Unfortunately the results of DPOAEs in our study were inefficient to detect the state of the population of OHCs.

Conclusions
The ABR abnormalities of prolonged IPLs and absent/dysmorphic wave V recorded in our XFG patients are previously undocumented observations that highlight the systemic nature of this condition and may lead to important clinical and research advances. These abnormalities reflect abnormal transmission that could cause peripheral as well as central auditory processing disorders. It is therefore reasonable to assume that the abnormal ABR responses together with the hearing loss that was confirmed in our study are indicative of either XFG-related changes in the central auditory nervous system or altered central activity due to changes in the output of the auditory periphery. Latency prolongation can result from slowing of the synaptic processes in the organ of Corti or decreased velocity in the first auditory neuron.

The ABR pathological findings (prolonged interpeak latencies I-V and prolonged interaural latency or absence of V wave) were more common in XFG than age-matched POAG patients and support the theory of an unknown retrocochlear causative factor located at the brainstem. It is conceivable that exfoliation material deposition in the organ of Corti or its vascular supply results in hearing loss, but this requires further investigation.

Future studies should investigate the possible involvement of the brainstem.

Author Contributions
Vassiliki P. Paliobei, substantial contribution in the research process and the conception, design, and writing of the article; Georgios K. Psillas, substantial contribution in the research process and the conception, design, and writing of the article; Dimitrios G. Mikropoulos, substantial contribution in the research process and the conception, design, and writing of the article; Anna-Bettina Haidich, major contribution, analysis and interpretation of data; Jannis Constantinidis, major contribution in revising the article, gave the final approval for publishing; Anastasios G. P. Konstas, major contribution in revising the article, gave the final approval for publishing.

Disclosures
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