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Evaluating the Hearing of Patients with Pseudoexfoliation Syndrome

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Background. It is estimated that pseudoexfoliation syndrome (PEX) occurs in 10–20% of the general population over 60 years of age, and its morbidity increases with age. Some research indicates that PEX may be a systemic disease. Some experts state that it can also lead to ear dysfunction.
Objectives. The aim of the study was to evaluate the incidence and type of hearing disorders in patients with PEX.
Material and Methods. The study included 51 patients (102 eyes) hospitalized in Wroclaw Medical University Hospital's Department of Ophthalmology and scheduled for cataract surgery in 2012–2014. Among these patients (whose age ranged from 55 to 92), 28 had PEX and 23 served as a control group. Both groups underwent ophtalmic examinations as well as ENT inspection and audiological tests (tonal audiometry, impedance audiometry, distortion product otoacoustic emission tests [DPOAE] and auditory brainstem response tests [ABR]).
Results. A statistically significant increase in the threshold of hearing in pure-tone audiometry was observed in PEX group for 2 kHz. In impedance audiometry tests, the stapedius reflex was identified in a greater proportion of patients in the PEX group than in the control group in all frequency ranges. There was no difference between the PEX groups and the control group in the results of the DPOAE and ABR tests.
Conclusions. PEX can be a systemic disease that affects the functioning of the inner ear causing sensorineural hearing impairment. The increased hearing threshold in pure-tone audiometry of the patients with PEX affects the speech range (mainly the frequency of 2 kHz). Impedance audiometry and pure-tone audiometry appeared useful in audiological diagnostics of patients with PEX (**Adv Clin Exp Med 2016, 25, 6, 1215–1221**).

Key words: hearing, hearing loss, pseudoexfoliation syndrome, presbyacusis.

Pseudoexfoliation syndrome (PEX) is a possibly-systemic age-related disease of unknown etiology [1, 2]. It is characterized by abnormal production and deposition of extracellular amyloid-like substance, mainly in the anterior segment of the eye [2, 3]. Electron microscopy and immunocytochemical studies have shown that pseudoexfoliative material (PXM) is also present in the connective tissue of blood vessels and such internal organs as the lungs, liver, kidney, bladder, meninges and inner ear [1–4].

It is estimated that pseudoexfoliation syndrome can be found in 60–70 million people over 50 years of age worldwide [3, 5]. Epidemiological data vary depending on the population. PEX is most frequent in Scandinavia, where it occurs in 20–25% of people over 60 years of age and 40.6% of those over 80 years of age [6]. The world average is 10–20% incidence in the general population over 60 years of age, and it increases with age [7].

PEX is usually first diagnosed by an ophthalmologist examining the anterior ocular segment using a slit lamp. Gray and white pathological deposits of fibrous material are visible in the front of the lens capsule, on the edge of the pupil and an-

terior chamber angle. PEX is one of the most common risk factors for secondary glaucoma, which can take a severe course not only due to high intraocular pressure, but also due to pseudoexfoliative damage of the elastic fibers of lamina cribrosa connective tissue that serve as a scaffold for the front of the optic nerve and its vessels [2, 8]. There are reports in the literature that PEX may also have a connection with systemic vascular disorders and diseases such as abdominal aortic aneurysms or Alzheimer's disease. Several studies have shown that compound PEX increases the risk of transient ischemic attack (TIA), stroke, hypertension and myocardial infarction [9–14].

There are also theories and studies indicating a link between PEX and sensorineural hearing impairment and balance disorders. Sensorineural hearing loss results from damage to the cochlear cells and/or the surrounding structures, as well as from disturbances in stimulus conduction quality in the auditory nerve and/or its interpretation in the central nervous system. Both the inner ear basal membrane and the anterior segment of the eye membrane are formed from ectoderm [1]. In some studies PXM has been found in the basal membrane of the inner ear [14]. The accumulation of extracellular substances can influence the ability to receive auditory stimuli, causing dysfunction of ear mechanoreceptors and consequently resulting in hearing loss [1].

In an epidemiological cohort study on aging carried out in the United States in 2011, the prevalence of hearing loss defined by audiometry increased steadily with age. According to that study, hearing impairment affects 11% of the population aged 44–54, 25% of those aged 55–64, and 43% of those aged 65–84 [15].

Presbyacusis is a physiological age-related hearing impairment of a sensorineural type, due to degenerative changes in the anatomical parts of the ear, both of the conductive parts of the outer and middle ear, and especially in the inner ear (the cochlea). However, the pathomechanism of presbyacusis has not yet been clearly defined. Multiple factors can influence the onset and severity of presbycusis. A genetic basis is considered a prominent factor, but the impact of comorbidities has also been the subject of many studies [16].

Material and Methods

The present study included 51 patients (102 eyes) admitted to Wroclaw Medical University Hospital's Department of Ophthalmology for cataract surgery in 2012–2014. Among these patients (whose age ranged from 55 to 92), 28 had PEX and 23 served as a control group.

Inclusion criteria were the absence of ear diseases in the interview, rational contact with the patient and (for inclusion in the PEX group) the presence of PEX in the anterior segment of the eye.

Exclusion criteria were a lack of rational contact with the patient, severe systemic disease making audiological examination impossible, ear infections, perforation of the tympanic membrane, previous exposure to ototoxic drugs or high noise levels, as well as inflammation of the upper respiratory tract.

Each patient underwent eye examinations, including examinations of best visual acuity on Snellen charts, intraocular pressure measurements, evaluations of the front and rear of the eyeball, and confirmation of the presence of the PEX syndrome on the front surface of the lens, iris or anterior chamber angle.

ENT assessment consisted of an interview, otoscopy and audiological tests, including tonal audiometry, impedance audiometry, distortion product otoacoustic emission tests (DPOAE) and auditory brainstem response tests (ABR). The audiological examinations were carried out in the Audiological Research Laboratory at Wroclaw Medical University. The equipment used included an AC30 clinical audiometer (Interacoustics A/S, Middelfart Denmark), Zodiac 901 middle ear analyzer (Madsen Electronics, GN Otometrics A/S, Taastrup, Denmark), Scout OAE system (Bio-Logic Systems Corporation, Mundelein, USA) and Sapphire 4Me Evoked Potential Response Unit (Teca Medelec, Oxford Instruments, Abingdon, UK).

The thresholds of hearing are divided into categories: normal hearing (0–25 dB), mild hearing loss (25–40 dB), moderate hearing loss (40–65 dB), severe hearing loss (70–85 dB) and profound hearing loss (from 85 dB or more) [17].

In the statistical analysis, Shapiro-Wilk's W test, the Mann-Whitney U test, the Friedman ANOVA and Dunn's test (*post-hoc*) were used for quantitative variables. For qualitative variables, Pearson's χ^2 test; and for 2 x 2 tables Yates's χ^2 test or Fisher's exact two-tailed test were used. Qualitative variables are shown in the tables as cardinality (n) and proportion (%). Quantitative variables are shown as mean (M), standard deviations (SD), median (Me), lower quartiles (Q1), upper quartiles (Q3) and extreme values (min, max). Test results were considered significant at a p-value < 0.05. STATISTICA v. 12 software (StatSoft, Tulsa, USA) was used for the analysis.

Results

The statistical analysis assessed the results of the audiological tests of 51 patients (including 37 women) aged 55–92 (mean M = 77.5; standard deviation SD = 8.1 years). The results were analyzed comparing two groups: patients with known pseudoexfoliative syndrome (the PEX group) and the control group. The groups were homologous in terms of sex distribution and age range (Table 1).

A statistically significant association between the presence of PEX and the results of the pure-tone audiometry test was observed for the 2000 Hz range: the proportion of normal-hearing ears was significantly higher in the control group than in the PEX group (35.7% vs. 13.0%, p = 0.008). A moderate degree of hearing loss occurred more frequently in patients with PEX (43.5% vs. 21.4%, p = 0.021). The degree of hearing loss in pure-tone audiometry tests was determined according to the scale edited by Śliwińska-Kowalska in "Clinical Audiology" [17]. The results are shown in Tables 2 and 3.

In impedance audiometry tests, the stapedius reflex was identified in a greater proportion of patients in the PEX group than in the control group in all frequency ranges. The greatest differences between the two groups were for the ipsilateral and contralateral threshold of the stapedius reflex (TH IPSI and TH CONTRA, respectively) in the 2000 Hz range. In the PEX group, the TH IPSI was significantly lower in the 4000 Hz range than in other frequency ranges; in addition, there was significant difference in the TH IPSI level between the 500 Hz range and the 1000 Hz range (90 vs. 85 dB; p = 0.006). In the control group, the only statistically significant difference (p < 0.05) was observed between the TH IPSI level in the 4000 Hz range and the other frequency ranges (Tables 4–6).

The tympanometry results showed that PEX patients more commonly had type As curves than the control group, but this trend was not statistically significant (Table 7).

The analysis of the ABR and DPOAE results in the two groups revealed that the PEX group and the control group did not differ in terms of latencies and interpeak latencies in the ABR test (p > 0.05), nor in terms of the incidence of outer hair cell responses in the DPOAE test in any frequency range (p > 0.05).

Table 1. Patients' characteristics

Feature (variable)	PEX n = 56		Control n = 46		p vs. C p
Age					0.553*
M ± SD	77.5 ± 7.6		77.7 ± 8.8		
Me (Q_1; Q_3)	78 (73; 83)		80 (72; 84)		
Min – Max	57 – 92		55 – 91		
Sex	n	%	n	%	0.343**
female	38	67.9	36	78.3	
male	18	32.1	10	21.7	

* Mann-Whitney test; ** Yates's χ^2 test.

Discussion

There are conflicting reports about the connection between PEX and other diseases, but the theory that PEX is a systemic disease has yet to be proved. Although many authors have found an association between PEX and vascular diseases or dementia [9–13], there are also studies that deny this correlation [8].

Most publications analyzing the state of hearing loss in patients with PEX have reported the presence of sensorineural hearing loss in these patients, but some studies were based only on subjective tests such as tonal audiometry. The current study also included objective methods of audiological diagnostics to evaluate most of the auditory pathway. Studies by Yazdani et al., Cahill et al., Shaban and Asfour, and Turacli et al. found an increased prevalence of sensorineural hearing loss in pure-tone audiometry at frequencies important for speech (1, 2, 3 kHz) in patients with PEX in comparison to patients without PEX in groups that were homologous in terms of age and sex [3, 18–20].

The results of the current study confirm this, mainly for the frequency of 2 kHz. Papadopoulos et al. also pointed out an association between PEX and hearing impairment, but in the high frequency ranges, particularly 8 kHz [21, 22]. In objective hearing tests like DPOAE and ABR, Paliobei et al. found that patients with PEX showed a greater prevalence of retrocochlear pathology [23]. In the present study, tonal and impedance audiometry were both used. The presence of stapedius reflexes was registered more often in patients with PEX than in the control group, which may indirectly indicate the cochlear etiology of hearing loss in patients with PEX. A particularly significant difference was observed for the 2 kHz frequency. The accumulation of deposits in the basilar and/or cover membrane of the cochlea is considered a possible pathophysiological mechanism of sensorineural hearing loss in patients with PEX, causing uneven transfer of energy to the hair cells. Perhaps the stiffening of the vibrating basilar membrane of the cochlea is most noticeable for this particular frequency.

Table 2. Comparison of the number of ears in the two subgroups and the quality of hearing in the frequency ranges analyzed

Pure-tone audiometry	PEX n = 56		Control n = 46		Pearson's χ^2 test
	n	%	n	%	p
250 Hz:					0.515
1. Normal	40	71.4	28	60.9	
2. Mild hearing loss	9	16.1	13	28.3	
3. Moderate hearing loss	6	10.7	4	8.7	
4. Profound hearing loss	1	1.8	1	2.2	
500 Hz:					0.055
1. Normal	42	75.0	24	52.2	
2. Mild hearing loss	7	12.5	16	34.8	
3. Moderate hearing loss	6	10.7	5	10.9	
4. Profound hearing loss	1	1.8	1	2.2	
1000 Hz:					0.092
1. Normal	19	41.3	37	66.1	
2. Mild hearing loss	14	30.4	11	19.6	
3. Moderate hearing loss	11	23.9	7	12.5	
4. Profound hearing loss	2	4.3	1	1.8	
2000 Hz:					**0.021**
1. Normal	6	13.0	20	35.7	
2. Mild hearing loss	16	34.8	21	37.5	
3. Moderate hearing loss	20	43.5	12	21.4	
4. Profound hearing loss	2	4.3	3	5.4	
5. Remnants of hearing	2	4.3	0	0.0	
4000 Hz:					0.242
1. Normal	10	17.9	10	21.7	
2. Mild hearing loss	14	25.0	7	15.2	
3. Moderate hearing loss	24	42.9	16	34.8	
4. Profound hearing loss	8	14.3	11	23.9	
5. Remnants of hearing	0	0.0	2	4.3	
6000 Hz:					0.067
1. Normal	5	8.9	3	6.5	
2. Mild hearing loss	5	8.9	10	21.7	
3. Moderate hearing loss	22	39.3	12	26.1	
4. Profound hearing loss	22	39.3	14	30.4	
5. Remnants of hearing	2	3.6	7	15.2	
8000 Hz:					0.114
1. Normal	1	1.8	1	2.2	
2. Mild hearing loss	6	10.7	9	19.6	
3. Moderate hearing loss	20	35.7	7	15.2	
4. Profound hearing loss	24	42.9	20	43.5	
5. Remnants of hearing	5	8.9	9	19.6	

1. normal (up to 25 dB); 2. mild hearing loss (25–40 dB); 3. moderate hearing loss (40–65 dB); 4. profound hearing loss (70–85 dB); 5. remnants of hearing (> 85 dB) [17].

Another theory is that deposits in vessel walls lead to an impaired blood supply to the inner ear [21]. This hypothesis is justified by the fact that the hair cells responsible for the perception of stimuli in high frequency ranges are the most sensitive to ischemia. However, it was not confirmed by the present study.

The current study, as well as the one by Erbek et al., found no difference in the functioning of the outer hair cells in the DPOAE tests in patients with PEX in comparison with the control group, despite the higher prevalence of sensorineural hearing loss in the PEX group [24]. However, this can be ex-

Table 3. Comparison of the number of ears in the two subgroups and the quality of hearing in the 2000 Hz range

Pure-tone audiometry	**PEX n = 56**		**Control n = 46**		**Test**
2000 Hz:	n	%	n	%	p
1. Normal	6	13.0	20	35.7	0.008*
2. Mild hearing loss	16	34.8	21	37.5	0.778*
3. Moderate hearing loss	20	43.5	12	21.4	0.021*
4. Profound hearing loss	2	4.3	3	5.4	0.796**
5. Remnants of hearing	2	4.3	0	0.0	0.158**

* Yates's χ^2 test, ** Fisher's exact two-tailed test.

Table 4. Results of stapedius reflex measurements

Feature (variable)	**Total n = 102**		**PEX n = 56**		**Control n = 46**		**p**
	n	**%**	**n**	**%**	**n**	**%**	
The presence of TH IPSI stapedius reflexes:							
500 Hz	74	72.6	43	76.8	31	67.4	0.404
1000 Hz	71	69.6	41	73.2	30	65.2	0.511
2000 Hz	61	59.8	38	67.9	23	50.0	0.104
4000 Hz	42	41.2	25	44.6	17	37.0	0.560
	p < 0.001		p = 0.001		p = 0.010		×
The presence of TH CONTRA stapedius reflexes:							
500 Hz	71	69.6	43	76.8	28	60.9	0.128
1000 Hz	69	67.6	42	75.0	27	58.7	0.124
2000 Hz	57	55.9	37	66.1	20	43.5	0.037
4000 Hz	30	29.4	18	32.1	12	26.1	0.653
	p < 0.001		p < 0.001		p = 0.002		×

Table 5. Results of *post-hoc* test – multiple comparisons of TH IPSI levels among patients in the PEX group

	500 Hz Me = 90 dB	**1000 Hz Me = 85 dB**	**2000 Hz Me = 90 dB**	**4000 Hz Me = 0 dB**
500 Hz	×	p = 0.006	p = 0.243	p < 0.001
1000 Hz	p = 0.006	×	p = 0.145	p = 0.007
2000 Hz	p = 0.243	p = 0.145	×	p = 0.002
4000 Hz	p < 0.001	p = 0.007	p = 0.002	×

Table 6. Results of *post-hoc* test – multiple comparisons of TH IPSI levels among patients in the control group

	500 Hz Me = 90 dB	**1000 Hz Me = 85 dB**	**2000 Hz Me = 40 dB**	**4000 Hz Me = 0 dB**
500 Hz	×	p = 0.204	p = 0.066	p = 0.003
1000 Hz	p = 0.204	×	p = 0.548	p = 0.008
2000 Hz	p = 0.066	p = 0.548	×	p = 0.030
4000 Hz	p = 0.003	p = 0.008	p = 0.030	×

Table 7. Tympanometry results

Curve type	Group				Total n = 102		Pearson's χ^2 test p
	PEX n = 56		control n = 46				
	n	%	n	%	n	%	
A	38	67.9	39	84.8	77	75.5	0.114
As	17	30.4	6	13.0	23	22.5	
Ad	1	1.8	1	2.2	2	2.0	

plained by the fairly advanced age of the patients participating in the study.

Myringosclerosis is hyalinization and calcification of the collagen layer in certain areas of the tympanic membrane. A clinical study conducted by Huang et al. showed a higher prevalence of myringosclerosis in women at more advanced ages; they found sclerosis most frequently in the tympanic membrane [25]. Cagdas believed that the movement of the tympanic membrane is hampered by lesions of sclerotic material, resulting in a decrease in amplitude in the patients' tympanograms without any effusion in middle ear [26].

Detorakis et al. noted that patients with PEX have shallower tympanometry curves, which could suggest deterioration of the elastic properties of the middle ear in PEX [27]. The results of the present study are consistent with those results, although the pathophysiological mechanism of hearing loss in patients with PEX suggested by Detorakis et al. seems rather unlikely.

The deposition of pseudoexfoliative material in the connective tissue of blood vessels and internal organs seems to be related to the physiological mechanisms of aging. It may likewise affect the aging of the organ of hearing, but the process needs further study.

Age-related hearing loss is highly prevalent and often untreated. The use of hearing aids or direct-to-consumer amplification is associated with improvements in cognitive, social, and physical functioning and therefore the quality of life [28].

The authors concluded that PEX may be a systemic disease that affects the functioning of the inner ear, causing sensorineural hearing loss. The increased hearing threshold in pure-tone audiometry tests of patients with PEX affects the speech range, mainly the 2 kHz frequency. Impedance audiometry and pure-tone audiometry seem to be useful in audiological diagnostics of patients with PEX. Detailed knowledge of the pathomechanism of hearing loss in patients with PEX requires further studies on larger groups of patients.

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